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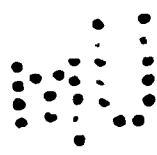
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DR. JAMES W. JOBLING, *President.*

THE GLYCEMIC REACTION, ITS CLINICAL SIGNIFICANCE, AND ITS RELATION TO IMMUNITY

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This article has been published in *The American Journal of Medical Sciences*, 1920, clix, 577, 853, and *Jour. Cancer Research*, 1920, Oct.

Discussion:

DR. GEYELIN: Dr. Rohdenburg presented such a vast mass of experimental detail that I find myself a little confused in trying to grasp it at all in the time given. There was one thing about the blood sugar curves in the experimental animals that I think is of some importance in interpreting the results, and that is, under what conditions of nutrition were the animals at the time the experiments were carried out? There is another point that I do not quite understand—the point Dr. Rohdenburg made about the significance of the types of the curves in the various clinical conditions. As I understood it, he said there was a distinct curve which had a definite relationship to immunity, and I do not see just what connection that had with the type of diseases he mentioned. I think the whole matter is an extremely interesting problem, and I agree with Dr. Rohdenburg that there is probably a great deal about it which is still obscure.

DR. MOSENTHAL: I feel somewhat as Dr. Geyelin does—that I have been presented with a mass of details which are difficult to grasp in a short time, but there are a few facts which seem worthy of consideration, because this question is of such very great importance.

In the first place, many of us depend largely on the type of blood sugar curve in making a diagnosis of incipient diabetes. The method that has been worked out by Hamman, Williams, Janney and others makes it evident that this is a very significant phenomenon. The normal blood sugar curve, after the ingestion of 100 grams of glucose, is, within certain limits, a perfectly definite one. A normal blood sugar curve will exclude the diagnosis of diabetes. It must be recognized, however, that a positive one may occur in diseases other than diabetes; such abnormal curves have been demonstrated in nephritis, hypertension, thrombo-angiitis obliterans, and undoubtedly they will be found in other conditions. The method of obtaining the blood sugar curve in the present communication will fail to demonstrate the maximal blood sugar in most instances, as the highest blood sugar level in normal individuals is reached before forty minutes have passed after the ingestion of glucose. Hence the observations in regard to the renal threshold for

glucose are only approximate. It is certainly true, as Dr. Rohdenburg has said, that the renal threshold is raised in many cases in which no renal disease or insufficiency can be demonstrated. If this problem is more thoroughly worked up, it may be of very great aid in the treatment of diabetes mellitus.

The type III reaction in this paper I believe really should be regarded as an extremely rapid type of normal curve. It is perfectly conceivable that within forty minutes the blood sugar may have risen as the result of glucose ingestion, and again dropped to the control or sub-control within this time.

The question of the relation of immunity and blood sugar is one of the most pressing problems in guiding the treatment of cases of diabetes mellitus that is confronting us. It is well established that the blood sugar of almost all diabetics may be reduced to normal, but is it advisable to do so? Should we sacrifice body weight and physical efficiency by the administration of low diets in order to bring the blood sugar to a normal level? If the immune reactions are rendered more efficient by reducing the blood sugar to normal a very definite answer to our question has been obtained. Whether the increased resistance reduced the blood sugar in these experiments, or whether the lowered blood sugar produced the increased resistance, is an open question. My own impression from the data presented to-night was that probably the increased resistance was responsible for the diminished blood sugar and not vice versa. This, if correct, would furnish the practical information that it is not worth while to diminish the blood sugar in order to increase the resistance.

I think it is worthy of note that usually those cases which have an unusually high blood sugar will have a tendency to have less of a rise in their blood sugar curve after the administration of glucose than those patients who have an initial low blood sugar. From that point of view it would seem that a high sugar level in the blood makes for a more efficient digestion of carbohydrate.

In closing I wish to express my admiration of the great amount of work so accurately and intelligently carried out by Dr. Rohdenburg and his associates.

DR. KAHN: The two previous speakers have the advantage of me in announcing the fact that the subject matter was too detailed and long to grasp by watching the slides. In fact, before I came to this meeting the program seemed to be rather mysterious. I saw no relation between glycemia and immunity. As to the production of glycosuria in animals by means of various endocrine substances which were injected, it is a known fact that the diet of animals previous to the administration of the endocrine substance influences the appearance of hyperglycemia and glycosuria, especially the presence or absence of calcium has a very marked effect on the production of glycemia. That is, if an animal has a high calcium intake previous to the administration of adrenalin or the xanthine bodies, etc., it is almost impossible to induce a hyperglycemia. If Dr. Rohdenburg would give us a résumé of the relations of hyperglycemia or hypoglycemia to immunity I would be very glad.

DR. STEVENS: I think this paper has opened up some very interesting

questions. It seems to me especially important if you consider that some of the reactions, hypo- and hyperglycemia especially, might be established during the process of immunity which can be likened to some of the other changes which take place in a patient during the time that he is having fever. If you take a case of pneumonia while immunity is being established, there is a great retention of salt. We know that this retained salt is distributed quite generally, and it seems to me that this shows that during the time the patient is developing immunity the production of the immune substances changes the permeability of the cells throughout the body, and that changes the relationship of the salts; that would come in very well with glyceimic changes at the same time. It seems to me that perhaps immunity in itself results in various changes in permeability that are produced by proteins. I know that in working with hemolysins the action of various sugars reduces the action of the hemolysins, especially if the hemolysins are those of the streptococcus, so it is possible that there is a great deal in this relation of the sugar to the permeability of the cell.

DR. ROHDENBURG: In answer to Dr. Geyelin's question in regard to the nutrition of the animals, they were starved for twelve hours previous to beginning the experiments. For several weeks before the test they received the usual laboratory diet which consists practically entirely of carbohydrates—bread, carrots, and once in four days, meat.

The time periods chosen and the curves plotted on these time periods were more or less arbitrary, and we were more or less driven to adapting them. If we compare "typical" diabetic curves as given in the literature, we find that there is no such thing. This confusion arises because some authors take blood specimens every fifteen minutes, and others continue their observations up to six hours. In brief, there is no regularity. We have not viewed the problem as a study in metabolism, but we have taken it purely as a functional test of endocrine activity.

As far as the relation of immunity to hyperglycemia is concerned, we cannot state whether the hyperglycemia which follows the repeated injection of a protein is the thing which produces the immunity, or whether it is simply a result of the general chemical process that occurs during the development of immune bodies. Whether hyperglycemia so induced is due to the increase in the temperature known to follow the injection of proteins, or whether it is due to the breaking up of the protein molecule, is also almost impossible to state. The interesting point is that the two phenomena run to some degree hand in hand. I do not believe that we can establish a direct relationship, but can only say that the two occur concurrently.

A CASE OF RIGHT-SIDED ENDOCARDITIS
(STREPTOCOCCUS VIRIDANS)

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The family history of this patient is negative. The past history is important in that it gives no history of rheumatism, and that the patient was rejected from the army twenty years ago for "heart trouble." He had gonorrhœa and soft chancre fifteen years ago, and sore throats about once every two years.

Present Illness: Up to one year ago this patient was perfectly well. Then trouble with teeth commenced for which he had to go to the dentist's. Several teeth were capped. He was then well again up to about eight months ago, since which time he has been ailing. The illness started with pain in the sacral region. This was followed by a pain in the splenic region, more marked on deep breathing, and accompanied by nosebleed. Two weeks later, he had a similar pain in the right side. Five months ago, he noticed that he was losing color. One month after this—in other words about four months ago—pain developed around the heart, and after persisting about a week disappeared, only to re-appear on the right side for a similar length of time. With this, pains and swelling developed in his ankles and then in the knees of both lower extremities, with fever, which he thinks has lasted ever since. In point of fact, all the symptoms which developed then have persisted during these four months until admission to the hospital—such as dyspnœa, frequency of urination, œdema of lower extremities and hemorrhagic spots. For the last month stools have been very dark.

Physical Examination: The patient is a weak, anæmic male. Over the entire body, more marked over the lower extremities, are numerous large and small petechiae. Toes and fingers are clubbed. Lungs show dullness, diminished fremitus and crackling râles over the right lower lobe. Heart is enlarged, with systolic thrill at apex, and systolic murmur over the entire precordium.

Blood Pressure: 147/48. *Blood Wassermann:* Negative. *Group;* II.

Blood Culture: *Streptococcus viridans*. 75 colonies per c.c.

Blood Count: W. B. C. 19,850. Polys. 78 per cent. Lymphos. 22 per cent.

R. B. C. 1,500,000–2,500,000. Hgb. 45–35 per cent.

Blood Urea: 0.25 gm. per liter.

Stool: Guaiac negative. No ova or parasites. Marked increase in urobilinogen and urobilin.

X-ray of Hands: Shows slight destruction and thickening of periosteum of the first phalanges of the 2d, 3d, 4th and 5th fingers.

Spinal Fluid: Clear, under pressure; culture negative.

Urine: Sp. Gr. 1010–12. Trace of albumin, with hyaline casts.

Autopsy: Aside from marked congestion of both *lungs* postero-inferiorly and several rather dense adhesions on both sides with a small amount of

pleural fluid in the right chest, the thorax shows no abnormalities except in the specimen I have to present this evening. The *liver* shows a cloudy swelling, and the *kidneys* a chronic nephritis.

Heart weighs 375 grams. The pericardium is smooth and glistening throughout. The muscle wall of the left heart at its thickest portion measures 2 cm. It is of good color, and shows no myocardial scars. The endocardium, aside from a few atheromatous plaques at the base of the mitral

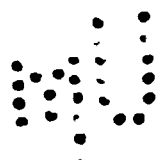
FIG. 1. Right heart. Vegetations on chordæ tendinæ and cusps of tricuspid valve.

valve, also shows no changes. The anterior cusp of the aortic valve on its ventricular surface shows a small firm vegetation in the region of the corpus arantii. Aside from a marked hypertrophy of the papillary muscles of this side, there are no other visible changes to be noted in the left heart. The right heart shows a slight dilatation of the right auricle. The foramen ovale is completely obliterated. The thickest portion of the right ventricular wall measures 1 cm. The tricuspid valve, at the line of attachment, is soft and pliable and free of any atheromatous plaques. As its free border

is approached, however, it becomes thicker and has numerous warty vegetations on both surfaces. (Fig. 1.) These vegetations are in some places firm and pearly white, and in others pinkish and rather friable, their size varying from 0.5 to 7 mm. The papillary muscles in the upper portion of the ventricle stand out quite prominently and show no fibrosis at all at their apices, where they are attached to the chordæ tendinæ of the posterior, or septal, cusp of the valve. This cusp also contains very few vegetations. The chordæ tendinæ of the other cusps are markedly thickened and matted together. This is especially true of those attached to the right or marginal

FIG. 2. Left heart. Defect in interventricular septum found between two adjacent papillary muscles.

cusps. Here the chordæ tendinæ arise from the apices of several papillary muscles, fused at their tips into a sclerotic mass of tissue. Between this mass of matted together chordæ tendinæ and the ventricular wall is found a pinkish laminated vegetation, measuring about 1 cm in thickness and 2 cm. in length. This overlies a perforation in the interventricular muscular septum, about 5 cm. from the apex of the heart and 3 cm. below the anterior cusp of the aortic semilunar valve,—in other words the perforation lies in the muscular interventricular septum. At its margins, the openings into this perforation on both sides of the heart are surrounded by very small pinkish vegetations, rather warty in character, upon a pale sclerotic rim. The en-



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period of two years. He regained his former strength, but a frequency in defecation began which persisted in spite of his sedentary habits. The stools were soft and pasty, and fluid at times. The bowel frequency was somewhat influenced by the diet. A high protein, or carbohydrate, diet had no noticeable influence upon the bowel movements, while a diet rich in fats invariably increased the frequency of defecation, and at times produced a severe enteritis which was only relieved by a radical change in the diet. Foods containing considerable admixture of insoluble material likewise produced a diarrhea. The patient became very susceptible to purgatives following the operation, a very mild purgative producing rapid and severe catharsis.

The patient's family history revealed nephritis in the father, but otherwise it was irrelevant.

The illness which brought him to the hospital was a rapidly progressive loss of strength and weight. During the last two months he had lost the sixty pounds which he gained after the operation, weighing when admitted only seventy pounds.

Physical examination revealed an extremely emaciated man. The intercostal spaces were deeply sunken. The abdomen was scaphoid and the extremities very small. The patient's mentality was good. The lungs were hyper-resonant but no râles were heard. The heart was negative. Upon the median line of the abdomen above the umbilicus there was an old operative scar. The liver was not enlarged. No areas of tenderness were elicited in the abdomen. A soft irregular mass was found in the hypogastric and umbilical regions, just left of the median line.

Blood pressure was 120/60.

Blood urea, 0.3 gm. per liter.

Blood Count: Red blood cells 3,900,000. White blood cells 11,600. Hemoglobin 80 per cent. Neutrophiles 70 per cent. Lymphocytes 29 per cent. Eosinophiles 1 per cent.

Stool examinations were made six times; at no time was blood demonstrated.

Urine showed a specific gravity of 1.020, a faint trace of albumin, and no sugar. Microscopically at times a few hyaline, granular, fatty and waxy casts were found.

Stomach contents: One fasting expression yielded 10 c.c. of thick brownish fluid containing bacilli and undigested food but no blood. The free hydrochloric acid was 0. Total acidity 20. After an Ewald test meal, 200 c.c. fluid was recovered containing undigested food, many bacilli, free hydrochloric acid, 0. Total acidity 6.

X-ray of stomach eleven days before death showed a regular indentation on the lesser curvature, not associated with the peristaltic wave on the greater curvature which was interpreted to mean a probable gummatous infiltration, or spasm indicative of an old ulcer in the pylorus and gastro-enterostomy. (Figs. 1 and 2.)

Course of last illness was progressively downward, the patient becoming asthenic. Glucose infusions were given without effect. The blood count

three days before death showed no change. The patient's temperature was normal until two days before death, when it increased to 101° C. The pulse rate was about 85 but increased to 140 just before death.

Clinical Diagnosis: Carcinoma of stomach.

Autopsy was performed three hours postmortem. The body was that of

FIG. 1. X-Ray immediately after a bismuth meal. Erect posture. Showing rapid emptying of bismuth into lower ileum and cæcum. This also shows the marked constriction of the pylorus.

a white man 175 cm. long, weighing seventy pounds and showing enormous emaciation. The superficial mucous membranes were pale. The muscles were soft and prominent, due to the marked emaciation. The abdomen was

scaphoid. In the median line above the umbilicus there was an old scar 14 cm. long. Median incision revealed little subcutaneous fat and muscle of a bright brownish red color. The peritoneum was smooth. The omentum was adherent to the anterior abdominal wall at the site of the previous operation. The colon was dilated with gas and the transverse colon showed considerable

FIG. 2. X-Ray four hours after a bismuth meal, showing only a small amount of the bismuth in the stomach, while the colon and ascending colon contain a large amount. Note prolapse and size of cæcum.

ptosis. The stomach and small intestines were collapsed. The appendix was apparently normal. The spleen and liver were small. The mesenteric lymph glands were enlarged. Upon close examination the transverse mesocolon was

rather short and the colon and stomach were situated very near together. The transverse mesocolon was penetrated by a loop of the ileum which was firmly attached to the greater curvature of the stomach. This loop of ileum was also adherent to the mesenteric border of the transverse colon. Pressure upon the cæcum forced gas through the ileocecal valve into the ileum

FIG. 3. Photograph of the stomach, ileum and cæcum, showing the gastroileostomy 6 cm. from the ileocæcal valve.

for 6 cm., and into the stomach. By constricting the opening into the stomach the gas was forced up the ileum. The esophageal end of the stomach was severed and water introduced; the fluid distended the stomach slightly but the greater portion flowed through a gastroileostomy opening at the greater curvature of the stomach (Fig. 3), and ran through 6 cm. of the ileum into

the cæcum. Very little of the fluid passed up the ileum from the enterostomy opening. When the stomach was opened its mucosa was covered with mucus and the mucosa appeared thickened. Upon the greater curvature 6 cm. from the pyloric valve there was noted a large gastroenterostomy opening which easily admitted the index and middle fingers. By separating the fingers one passed down the ileum and the other up the ileum. The opening down the ileum was the larger and more direct. Between the fingers a transverse groove of scar tissue was felt. Externally the gastro-ileal junction was perfect, showing no irregularities nor adhesions. The pyloric opening of the stomach admitted a probe 0.3 cm. in diameter. When the pyloric ring and duodenum were opened the mucosa of the duodenum near the valve showed a papillary adenoma 1 cm. long. The remainder of the duodenal mucosa was unaltered. The bile ducts were patent. The muscular walls of the duodenum were hard and thickened, and externally there were some firm adhesions which constricted the lumen near the pyloric valve. The jejunum and ileum were empty, and apparently smaller in diameter above the anastomosis than below it. The colon was dilated and its mucosa presented numerous mucous folds not unlike the plica intestinales of the small intestines. The lymph follicles of the colon were hypertrophied.

The only other pathology worthy of note was, briefly, a small heart with a relatively hypertrophied left ventricle; right apical pleuritic adhesions; terminal broncho-pneumonia; atrophic spleen and fatty liver; a marked chronic glomerulo-nephritis with both kidneys small, granular and a combined weight of only 130 gm. Both contained numerous small cortical cysts.

Microscopic sections through the gastroileostomy union showed the immediate gastric mucosa excessively infiltrated with mononuclear cells and the immediate mucosa of the ileum showed a similar condition. The epithelium seemed uninterrupted from the mucosa of the stomach to that of the ileum with intestinal glands over the site of the anastomosis. No marked differences were recognizable between the mucosa of the ileum above the anastomosis from that below the anastomosis and in the functioning part of the intestines. The muscular coats presented a band of hyaline scar tissue at the point of the operation. The muscularis mucosæ in the functioning portion of the ileum appeared hypertrophied.

The kidneys showed an extensive chronic glomerular nephritis with relatively few apparently functioning glomeruli present. The presence of the nephritis, clinically, was not suspected, as the blood urea was only 0.3 gm. per liter with a faint trace of albumin and few casts present in the urine without other nephritic symptoms.

The short-circuited alimentary tract was not diagnosed ante-mortem, and no studies upon the patient's utilization of the dietary elements were made. A brief review of the rather extensive studies upon the utilization of food following resection, or short circuiting of the intestines is of sufficient interest, and follows.

In the works of Flint (1), Erlanger and Hewlett (2), Carrel, Meyer and Levene (3), and Underhill (4), excellent contributions have been made upon the metabolism after resection, or short circuiting, of the small intestines. Flint's studies consisted chiefly of the morphological changes found as a result of abbreviating the intestinal tract and he reported chiefly a transverse hypertrophy involving the muscularis mucosa of the remaining functioning intestine and an apparent atrophy of the non-functioning part. His observations are in accord with those of Cunningham upon this same condition. Flint noted a hypertrophy of the villi and glands of the functioning intestines but no hyperplasia of these structures was observed which is contrary to the statement of Monari, who noted a hyperplasia of the villi and crypts in the remaining part of the intestinal tract following a resection. Flint also noted an increase in the size of the epithelial cells of the glands and many goblet cells were observed in the crypts of the mucosa. This compensatory hypertrophy, Flint concludes, makes it probable that in favorable cases approximately the original epithelial area of the intestine is restored. He further states that the stomach and colon have no power of adaptation to assume the function of the small intestine, although in some cases a marked dilatation of the stomach was observed. The other organs remained unaltered microscopically and macroscopically. Flint's observation upon the metabolic changes following resection, or short circuiting, of the small intestines showed that as much as 50 per cent. of the total amount in a dog may be removed without fatal results, the animal gradually returning to its normal weight and metabolism when upon a favorable diet under good conditions. Removal of 75 per cent. or more, is not necessarily fatal, but such animals rarely show a true recovery. At first the animals suffer from a severe diarrhea and have an enormous appetite and an intense thirst. They lose body weight and remain intensely sensitive to unfavorable conditions of diet and living. They may eliminate as much as 66 per cent. of the food eaten. Compensation, however, will be established upon a rich, easily consumed diet. Any

increase in the amount of fats in the food may lead to an increased elimination of fats and nitrogen to about 25 per cent. above normal.

Underhill found that as much as 39 per cent. of the small intestines of a dog may be short circuited without causing significant detrimental changes in the utilization of the various food stuffs, and the animal may gain in weight. This was equally true when the observations were made at a period shortly after operation, or at a period several months later. When as much as 66 per cent. of the small intestines was functionally resected the nutritive condition of the animal was affected. The fat utilization was decreased and the dog displayed a decided tendency to furnish a negative nitrogen balance. There was a small but progressive loss of weight. The food utilization was in general apparently better immediately after the operation than later. In neither of the above animals did a natural increase in fat intake cause significant changes in the utilization of this, or other food-stuff.

When about 75 per cent. of the small intestines of a dog were short circuited, food utilization was more seriously impaired, at least at a period several months after the operation. This is particularly true for fat utilization.

All of these animals displayed a greater ability to utilize carbohydrates than does a normal dog, even though the carbohydrate intake is large. Carbohydrate utilization was complete either shortly after the operation, or months later. This ability to utilize carbohydrates has been a uniform finding among most of the observers.

Over forty human cases are reported in the literature where large portions of the small intestines have been resected and upon whom metabolic studies have been made. Human cases behave in general like the lower animals and show the similar clinical and metabolic disturbances. Noteworthy are the cases of Panchet (5), Axhausen (6), Storp (7), Denk (8), Fantino (9), Zeidler (10), Zusch (11) and others. Zusch (11) reported a case where 316 cm. of the small intestines was functionally re-

sected in which 13.7 to 21.3 per cent. of the diet nitrogen, 18.1 to 38.5 per cent. of the diet fat, and no carbohydrate foods were found in the feces, without evidences of intestinal putrefaction. Other reports show varying degree of functional disturbances in patients following extensive resection. The disturbances may consist simply of a frequency of bowel movements to severe diarrheas of large watery stools. Again some gain in weight and strength while others die from inanition.

The interesting physiological features in our patient were the gain in weight and strength for a period of three years after the operation, without apparent clinical symptoms save a frequency in bowel movement and an increased susceptibility of the intestinal tract to diets rich in fats and indigestible material, also an apparent tolerance for carbohydrate foodstuffs. In the last two years the sensitiveness to a change in diet became exaggerated, associated with a progressive loss of weight and of strength, with an intense desire for food and water. This change probably was the result of a gradual closure of the pyloric passage with an increased loss of small intestinal surface until practically only the terminal 6 cm. of the ileum was functioning.

This case is another one of the rare instances in medicine where a large amount of animal experimentation is to some extent confirmed by the observation of a human case.

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EXPERIMENTAL STUDIES IN ENCEPHALITIS
LETHARGICA

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During the course of investigations carried on within the past year, Strauss, Hirshfeld and Loewe (1), and Loewe, Hirshfeld and Strauss (2) demonstrated that epidemic encephalitis was due to a filtrable virus. This naturally suggested the application of methods for the cultivation of the filtrable virus. Our early findings on the organism were embodied in a brief preliminary note which appeared in the *Journal of the American Medical Association*, 1919, lxxiii, 1056 (3). It is our intention to present the experimental work upon which the preliminary report was based and to report additional investigations carried on since that time.

Pathology

The gross appearance of the brain of a case of encephalitis is characterized by intense congestion of the pia-arachnoid, and there are small areas which seem to be deposits of fibrin upon the pia.

The histology of acute epidemic encephalitis or encephalitis lethargica is very similar, if not identical, to that of acute poliomyelitis. The difference between the two diseases is chiefly one of degree and localization of the lesion. The principal feature is a round cell infiltration of the so-called perivascular space or more correctly the Virchow-Robin adventitial space. The veins are more affected than the arteries. In relation to the vessels there are foci of small round cells of varying extent which are probably formed by the migration of these cells from the vessels into the parenchyma. Very frequently there are minute hemorrhages and occasionally the hemorrhages are of macroscopic size. In one case there was a hemorrhage of considerable extent in the

centrum semiovale which had ruptured into the ventricle. There are areas of edema and microscopic areas of necrosis. The meningitis is characterized by the presence of small round cells. The lesions occur not only in the cerebrum, pons, and medulla, but also in the cord and the posterior root ganglia.

While it is doubtful whether there is any difference between the histology of encephalitis and poliomyelitis, a distinction can be made between the two diseases in the localization of the lesions. The meninges of the cerebrum are more affected in encephalitis than in poliomyelitis. In poliomyelitis it is rare to find extensive lesions in the cerebrum, while in encephalitis the basilar ganglia and midbrain are markedly affected. The pons and medulla are involved in both diseases about equally.

Pathology of Animals

The brains of both monkeys and rabbits are intensely congested. There is a meningitis of varying intensity but always characterized by a predominance of small round cells. In many cases polymorphonuclear leucocytes are almost entirely absent in the inflamed pia. The vessels are dilated and congested. In some of the rabbits, especially those injected with 1 c.c. of spinal fluid, there are extensive subpial hemorrhages. The lesions in the brain are similar to those found in the human, namely, infiltration of small round cells in the Virchow-Robin spaces, focal infiltrations, microscopical hemorrhages, areas of necrosis, and edema. In some of the rabbits there are microscopical areas of focal necrosis in the subcortex in which there are peculiar cells the exact nature of which we have not as yet determined. In some of our animals the most marked lesions occurred in the basilar ganglia, pons, and medulla, and this is especially true of a monkey and rabbits inoculated with the germ. The filtrate from the nasopharyngeal membrane of a fatal case named "W" when injected intracerebrally into rabbits, killed the animals very quickly and produced a meningitis and extensive hemorrhages. Subsequent inoculations of filtrates of these brains into other rabbits caused an apparent lessening of virulence of the virus, the

rabbits lived longer, and the lesion became less hemorrhagic and more typical until finally we obtained the classical picture of small round cell infiltration in the Virchow-Robin spaces, and focal infiltrations with very few, if any, hemorrhages. This particular virus therefore produced in the rabbit, first, a pathological picture of a hemorrhagic encephalitis and subsequently the lesion which we are accustomed to regard as more characteristic of epidemic encephalitis.

As is well known to investigators, rabbits that die as the result of experimentation, show very few symptoms of disease before death. They are usually found dead by attendants who make rounds of the cages. This has been true of all of our inoculated rabbits with two exceptions:

R. 29, which had received a filtrate of the brain of monkey 12, was discovered apparently dead by the attendant and placed in the ice box. Fortunately we were notified of its demise and went to autopsy it. We found the rabbit was still alive, but the respirations were so shallow that it was not surprising the attendant was deceived. The animal lay on its side with eyes closed, legs extended and head drawn back. We kept it alive four days by feeding it by gavage. It died in a convulsion. The virus from this rabbit's brain was carried through four generations.

R. 52 presented a similar clinical picture and we kept it alive by gavage for six days. The virus from its brain was carried through three generations.

The picture presented by these two rabbits was strikingly like the lethargy we have observed in our human cases.

Inoculation Experiments

We began our experiments March 1, 1919, by inoculating a *Macacus rhesus* monkey subdurally and intraperitoneally with a saline emulsion of human brain from an encephalitis case. The following day the animal was ill and its spinal fluid contained 90 mononuclear cells per c. mm. Two days later, fearing that the animal might survive, we killed it. Sections of the brain showed

multiple cortical and subcortical punctate hemorrhages, and microscopically there was perivascular infiltration of mononuclear leucocytes and a moderate degree of meningitis shown by an infiltration of small round cells. An emulsion of this monkey's brain was then injected intraperitoneally and *intracerebrally* into another *Macacus rhesus* and no symptoms developed until six days later when the animal became paralyzed on the side opposite the site of injection. It was killed seven days later, or thirteen days following inoculation, and there was found a large hemorrhage surrounded by an area of necrosis at the site of the injection which had been made in the neighborhood of the motor pathway. The half of the cerebrum which contained the lesion was put in formalin and the other half in 50 per cent. glycerin in cold storage. Two months later sections were made and showed the presence of a meningitis with mononuclear cells and of perivascular infiltration around vessels at a distance from the hemorrhagic and necrotic area. (See figs. 4, 5, and 6.) This convinced us that the inoculation had probably been successful. We therefore made an emulsion of the glycerinated brain and inoculated a monkey intracranially. Aside from a slight apathy this monkey showed no symptoms. Two rabbits were inoculated with the same emulsion: both died. One showed no cerebral lesion, but the other showed the typical lesions of encephalitis. We had therefore succeeded in transmitting the virus through two monkeys and a rabbit and had further proved that the virus remained viable for two months in 50 per cent. glycerin. It became evident also that the monkey was not very susceptible to the virus obtained from the brain and that inoculation from brain to brain was difficult, and that the virus of the disease resided in the naso-pharynx. The next logical step was for us to investigate along this line.

We chose a case where the nasal discharge was very profuse, thick and mucopurulent. This discharge was emulsified with saline solution and passed through a Berkefeld filter "N." Cultures on ordinary media showed it to be sterile. A *Macacus* was inoculated intracranially and intraperitoneally. Eight days later

both hind legs were paretic and the animal was distinctly apathetic. Fourteen days after inoculation the spinal fluid contained 16 cells per c. mm., mostly lymphocytes. By the eighteenth day it had completely recovered. Two months later this animal was inoculated intracranially with a filtrate of nasal mucous membrane which had produced lesions in monkeys and was very virulent for rabbits. We used what we judged to be three times the lethal dose. The animal gave no evidence of disease. It had probably acquired an immunity.

Having found the virus in the nasal discharge it was decided to use the naso-pharyngeal mucous membrane of a fatal case for inoculation. This was ground up in a mortar in saline solution and filtered through a Berkefeld filter "N." The filtrate was found to be sterile on ordinary media and on April 7, a *Macacus* was inoculated intracranially and intraperitoneally. The following day there was a right hemiparesis and paresis of the left external rectus. Three days later there were typical Jacksonian convulsions of the right side which later became general, and stupor. These convulsions continued two days and the animal became very weak. It was killed on April 13, six days after inoculation. There were numerous cortical and subcortical hemorrhages; one on the surface of, and a large one within, the pons. There was some necrosis and glia cell increase near the hemorrhage. The pathological picture was that of a hemorrhagic encephalitis. An emulsion of this brain was injected intracranially into another monkey and two days later there was paresis of the right arm and leg. The animal was then killed and the brain showed intense congestion, a large hemorrhagic area surrounded by numerous cortical and subcortical punctate hemorrhages, and a small area of necrosis in the center of the large hemorrhage. Again the picture of a hemorrhagic encephalitis. While in these two monkeys the typical histological picture of epidemic encephalitis was not present, we believe the lesion was due to the virus of the latter disease, for as pointed out before, we have experimental proof that the virus can first cause hemorrhages and then later probably through loss of viru-

lence produce the typical histological picture of mononuclear meningitis, perivascular, and focal infiltration of small round cells.

We inoculated another monkey with the filtrate of naso-pharyngeal mucous membrane. It developed a paresis of both hind limbs, and was very ill for four weeks and then recovered. Another monkey was inoculated with the same filtrate after it had been kept in 50 per cent. glycerine in cold storage for two months. It showed marked excitability, ruffled fur, and paresis of left foreleg. It recovered in four weeks.

Control Experiments

One monkey was inoculated with 2 c.c. of the filtrate from the nasal washings of a case of influenza complicated with sinusitis and broncho-pneumonia with a negative result.

Three other monkeys were inoculated intracranially with filtrates of naso-pharyngeal mucous membranes from cases which died from surgical diseases. They were all negative.

Our investigation soon showed that rabbits were much more susceptible to the virus than monkeys. By the time we discovered this it was too late to try inoculation of human brain emulsions in these animals. Recently we have obtained fresh material from the cases, and the following results were obtained.

| | No. Cases | Rabbits In- oculated | No. Dead | No. Rabbits with Lesions |
|--------------------------------|-----------|-------------------------|----------|-----------------------------|
| Filtrate of human brain. . . . | 3 | 12 | 4 | 3 |
| Emulsion of human brain. . | 2 | 6 | 4 | 2 |

The filtrate from the nasopharyngeal mucous membrane of a fatal case has been inoculated in a rabbit intracranially and produced typical lesions. This virus has been transmitted through six rabbits, the filtrate of a brain emulsion being used each time. It was then transmitted successfully to a monkey and back to the rabbit for two transmissions. We then stopped because we could see no reason for further propagation.

A glycerinated filtrate of nasal pharyngeal mucous mem-

brane which had been kept in cold storage for two months has been transmitted successfully through three rabbits, and the same filtrate which had been kept four months in cold storage was transmitted through four rabbits. This virus was the one which first caused hemorrhagic lesions and subsequently in later rabbits the typical lesions.

Control Experiments

Filtrates of nasopharyngeal mucous membrane of five fatal cases dying from surgical conditions and one case dying from mediastinal tumor were injected intracranially in rabbits with negative results.

We have taken the naso-pharyngeal mucous membrane of rabbits succumbing to inoculations of the virus and made filtrates which have been inoculated into rabbits with positive results. As controls to these experiments, we have inoculated seven rabbits with filtrates of nasopharyngeal mucous membrane of rabbits with negative results.

Our investigation seems to point rather conclusively to the nasopharynx as the portal of entry of the infection and in the few experiments which we have made thus far it seems also indicated that the virus can be excreted by the nasopharynx. Our clinical experience likewise points to the nasopharynx as the portal of entry for the infection. Many of the cases give a history of coryza and sore throat before the onset of the symptoms of encephalitis and not infrequently the symptoms of a mild sinusitis are complained of. We have seen three cases where a specialist on diseases of the nose and throat had been consulted because of the nasal discharge and pain in the face, and suspected a mild sinusitis which was probably present though subsequently the development of the symptoms of encephalitis made the case clear.

Normal saline solution is used in washing the nasopharynx and the solution is filtered through Berkefeld "N" very shortly after it is obtained. The filtrate is then cultured on ordinary media and if sterile 1 c.c. is injected intracranially into two or three rabbits. The results of these inoculations are as follows:

| No. Cases | No. Rabbits Injected | No. Rabbits Dead | No. Rabbits with Lesions | Diag. Made in Cases | Time | Average | Per Cent. |
|-----------|----------------------|------------------|--------------------------|---------------------|----------|---------|-----------|
| 18 | 38 | 28 | 17 | 14 | 1-7 days | 3 days | 78 |

The inoculation intracranially into rabbits of filtrates of nasopharyngeal washings has become in our hands a method of diagnosis. As noted it is a method which gives a positive result in 78 per cent. of cases. There are cases of encephalitis which do not present the classical symptoms of encephalitis and it is in such cases that rabbit inoculation has been especially valuable.

Spinal Fluid Inoculations

Inoculation of spinal fluids has demonstrated that the virus is present in the fluid. One *Macacus rhesus* received intracranially 2 c.c. of the spinal fluid of a fatal case of encephalitis, and developed a paresis of the right hind leg. It showed very marked motor excitability which was followed by a period when it was very apathetic. It appeared ill for four weeks but completely recovered at the end of six weeks. Another monkey received 2 c.c. of spinal fluid which had been kept on ice for nineteen days, and which had been obtained from a case which subsequently recovered. This inoculation was negative.

Inoculations into rabbits proved more successful and we have used this method in conjunction with inoculation of nasal washings for diagnosis. The results of these experiments are as follows:

| No. Cases | No. Rabbits Injected | No. Rabbits Dead | No. Rabbits with Lesions | Diag. Established | Time | Average | Per Cent. |
|-----------|----------------------|------------------|--------------------------|-------------------|----------|---------|-----------|
| 26 | 56 | 38 | 22 | 16 | 1-8 days | 3 days | 61 |

As a control we inoculated ten rabbits with spinal fluid from cases of cerebral neoplasm, uremia, brain abscess, and psychasthenia. These inoculations were negative.

In the beginning we inoculated rabbits with 1 c.c. of the spinal fluid from encephalitis cases and found that the animals died within 12 hours and showed nothing but congestion or sub-

pial hemorrhages, but not the typical histological lesions. We then reduced the dose to $\frac{1}{4}$ c.c., the animal lived longer, and we obtained the definite pathological picture. It would appear from this that the spinal fluid of these cases contains some toxic substance to which the rabbit is very susceptible, but we have not as yet been able to determine its nature.

Relationship to Poliomyelitis

When the epidemic of acute encephalitis first made its appearance in England opinion was divided as to whether one had to deal with botulism, poliomyelitis or a new disease. Botulism was quickly ruled out, and later it was seen that the clinical picture was not the same as that with which physicians had become familiar in the epidemics of poliomyelitis in recent years. The predominance of cerebral symptoms, and under this category are to be included the basilar ganglia and mid-brain, indicated either a new disease entity or a modification of the poliomyelitic virus, both as to its virulence and its affinity for the bulb and spinal cord. Our investigations seem to prove that we are dealing with a new clinical entity. We have found in our inoculations of monkeys both with virus and with cultures of the organism that they are extremely refractory. Some of the animals have become ill and then recovered, others have shown no evidence of illness. As is well known, monkeys are peculiarly susceptible to the virus of poliomyelitis and generally succumb to the inoculation. It is unusual for them to recover and have a natural immunity. Marks succeeded in infecting rabbits with inoculations of poliomyelitis virus. He did not produce the typical lesion of poliomyelitis, but was able to transfer the disease from rabbit to monkey. It appears from his experiments that the rabbits acted as a host for the virus. Our investigations show that rabbits are very susceptible to the virus and organism of encephalitis, although approximately 50 per cent. appear to have a natural immunity. Those that do succumb show the lesions which are typical of the disease. No one so far as we are aware has ever succeeded in producing poliomyelitis experimen-

tally by inoculation of spinal fluid. We have succeeded, not only in our inoculation experiments, but also in isolating the organism from the spinal fluid. Therefore we feel justified in concluding not only on clinical grounds, but also from our animal inoculations and cultures, that acute epidemic encephalitis and acute poliomyelitis are two distinct diseases.

Relationship to Influenza

During the epidemic of influenza in the fall of 1918, there were a number of cases of encephalitis. These cases increased in frequency, however, during the months of January, February and March, 1919, after the peak of the influenza epidemic had been reached. During the summer there appeared a number of sporadic cases of encephalitis, and in the early fall the number appeared to be on the increase, until the onset of the second influenza epidemic when there was a marked rise in the incidence of the disease. However, just as in the previous year, so again it has been noted that the greatest number of encephalitis cases appeared after the influenza epidemic had reached its height, and was on the wane. Many of the cases of encephalitis give a history of previous influenza infection antedating the onset by a period varying from a few weeks to a few months. Some cases have developed during the convalescence period of what had been diagnosed as an influenza infection. It would appear, therefore, that either influenza bears some etiological relationship to encephalitis, or that it renders individuals apparently more susceptible to the disease, or that the two appear to run a synchronous course.

The animals in which we have produced encephalitis have shown no lesions which we can consider of the nature of influenza. It is extremely difficult to determine the relationship of these two conditions until we know definitely what is the etiological factor in influenza. In three cases we have isolated from filtrates or nasopharyngeal washings, organisms in pure culture which closely resemble morphologically the organism found in our encephalitis series. This work is now being prosecuted

FIG. 1. Human brain. Mononuclear cell infiltration and congestion of vessels in meninges of cerebrum.

vigorously, to establish a possible etiologic relationship. Thus far no encephalitis has been produced in rabbits with these strains.

Cultivation of Organism

The negative results of our early cultural studies using ordinary laboratory media for aerobic and anaerobic culture, as well as the Rosenow technic, soon convinced us that we were dealing

FIG. 2. Human brain. Focal infiltrations with mononuclear cells in the putamen (lenticular nucleus).

with an organism of very discriminating cultural requirements. This led us to the adoption of the tissue ascitic fluid medium introduced by Smith, popularized by Noguchi and so successfully used by him for the cultivation of *Treponema pallidum* and other

organisms, and by Flexner and Noguchi in growing the globoid bodies of poliomyelitis. The original Noguchi technic has been followed closely, the various modifications which suggested themselves having been found unsatisfactory. The preparation of the medium as now used is briefly as follows:

Sterile kidney fragments are transferred to tubes 20 cm. x

FIG. 3. Human brain. Mononuclear cell infiltration in the Virchow-Robin and perivascular spaces of vessel in the tegmentum of the mid-brain.

1 1/2 cm., covered with 3 to 4 c.c. of sterile ascitic fluid, and incubated for 48 hours. At the end of this time the contaminated tubes are detected by gross examination and by dark field illumination and forthwith discarded. The sterile tubes are then inoculated and ascitic fluid added to form a column about 10 cm. high. Vaseline of a low melting point is heated and poured over

the surface of the fluid in a layer about 1 cm. thick. The vaseline quickly cools and effectually seals the tube thus producing almost perfect anaerobic conditions.

Control tubes are set up as follows: (1) Serum and vaseline, (2) inoculum, serum and vaseline, (3) serum, kidney and vaseline. Both controls and inoculated tubes are incubated at 37° C.

FIG. 4. Monkey brain. Edema, necrosis and adventitial infiltration of vessel in cortex. Animal injected intracerebrally with emulsion of brain of monkey successfully inoculated with infected human brain.

The optimum solid medium is of a gelatinous consistency, made so by the addition of one part of 2 per cent. nutrient agar to four or five parts of ascitic fluid, the kidney tissue being added as usual. The customary controls are also made.

The materials cultured were as follows:

1. Fragments, saline emulsions, and Berkefeld filtrates of saline emulsions of brains of humans and of experimental animals. Brain material was taken preferably from the mid-brain where the most pronounced lesions of this disease are found. Material for inoculation was removed under the strictest sterile precautions and with the brain *in situ*. Grossly contaminated

FIG 5. Monkey brain. Cortex showing perivascular infiltration of mononuclear cells. Animal same as that pictured in Fig. 4.

material has been stored in the refrigerator in 50 per cent. glycerin, and subsequently cultured *en bloc* or ground up and filtered.

2. Cerebrospinal fluids removed under sterile precautions from patients and experimental animals were cultured in amounts from 0.5 to 1.0 c.c.

3. Nasopharyngeal washings from living patients were fil-

tered through the standard 5N Berkefeld or Mandler filters. Nasopharyngeal mucous membranes removed at autopsy from humans and experimental animals were finely emulsified and filtered.

All filters used held back *B. prodigiosus* under the same conditions obtaining in the experimental filtrations. All filtrates

FIG. 6. Monkey brain. Cortex showing perivascular infiltration with mononuclear cells. Animal same as that pictured in Fig. 4.

before being used were cultured on ordinary laboratory media to insure sterility.

Control studies were carried out on nasal washings, nasopharyngeal mucous membranes, cerebrospinal fluids and brains of patients suffering from or dead of diseases other than lethar-

gic encephalitis. The nasopharyngeal mucous membrane and brains of normal rabbits were also studied.

In spite of the numerous precautions used in the preparation of the culture tubes, a small percentage of contaminations invariably appear. Most contaminations are detected grossly, by

FIG. 7. Monkey brain. Mononuclear cell infiltration in Virchow-Robin space (adventitia). Pons. Animal inoculated with emulsion of brain from human case.

dense clouding of the medium, gas formation, evidence of putrefaction, and the rapid disintegration of the kidney. Others are discovered on dark field illumination and examination of smears stained by the Gram method.

A successful growth is usually manifested on the fifth to the seventh day by clouding of the medium commencing about the

kidney tissue, the outline of which becomes hazy and irregular. The clouding extends rapidly upward to within about 1 cm. of the top of the ascitic fluid column. The organisms are not held in suspension long but tend to form clumps which settle to the bottom of the tube, leaving the supernatant fluid clear. The

FIG. 8. Rabbit brain. Mononuclear cell infiltration in the meninges of the cerebrum. Animal injected with Berkefeld filtrate of nasopharyngeal mucous membrane from a fatal human case.

clouding of the medium is due partly to the growth of the organism itself, and partly to protein precipitation due to the acid produced by the organisms.

Transfer to solid medium can be obtained only with the later generations of the organism. The growth in solid medium assumes different forms depending on the adaptability of the given

strain to this type of culture medium. When the organisms are numerous a diffuse clouding is observed, most marked about the region of the kidney and extending upward. When the organisms are fewer in number, minute colonies appear only in the region of the kidney or occasionally scattered throughout the medium. The colonies gradually increase in size so as to become recognizable with the naked eye.

FIG. 9. Rabbit brain. Perivascular infiltration (principally mononuclear cells) of vessels in the mid-brain. Third transmission in rabbit of virus originally derived from human nasopharyngeal mucous membrane.

Studies of fluid cultures under dark field illumination reveal the organism as minute globular refractile forms, occurring singly, in diplo-form, chains and clumps, the latter form predominating, especially in the older cultures. These bodies show active Brownian motion but no true motility.

In stained smears the organisms appear as minute globular bodies which are arranged singly, in diplo-forms, in chains and clusters. The organism has an average diameter of 0.25 micra as measured by the ocular micrometer. The reaction to the Gram-stain depends a great deal on the medium used and on the age of the individual culture. Young cultures and those grown

FIG. 10. Rabbit brain. Area of focal necrosis in proximity to vessels showing the perivascular infiltration. Mid-brain. Fourth transmission in rabbit of virus derived from human nasopharyngeal mucous membrane.

on fluid medium are mostly Gram-positive, while older cultures and those grown on solid media tend at times to be Gram-negative. The organisms stain well with prolonged staining in Giemsa, Loeffler's alkaline methylene blue, Unna's alkaline methylene blue (old) or Ljubinsky's pyoktanin-acetic acid, after fixa-

tion in methyl or absolute alcohol. These several stains have proved valuable in establishing a definite tinctorial reaction for the organism which is basophilic in nature.

The organism has been recovered in pure culture from Berkefeld filtrates of the nasopharyngeal mucous membrane of four

FIG. 11. Rabbit brain. Area of focal infiltration with mononuclear cells in the basilar ganglia. Animal injected with Berkefeld filtrate of brain of monkey successfully inoculated with virus derived from human nasopharyngeal mucous membrane, and which had been transmitted through four generations in rabbits.

human cases of epidemic encephalitis. We succeeded in all of four attempts. One of these strains has been carried on artificial culture medium without animal passage to the fifteenth generation; another to the tenth. Later strains have proven pathogenic

for animals. Controls prepared with filtrates of nasopharyngeal mucous membrane of humans dying of such conditions as cardiovascular disease, megacolon, peritonitis, mediastinal tumor, carcinoma of the stomach, post-operative hemorrhage and empyema have all been sterile.

FIG. 12. Rabbit brain. Area of mid-brain showing perivascular infiltration with round cells. Same animal as Fig. 11.

Filtrates of nasal washings from seventeen cases of epidemic encephalitis were cultured with positive findings in eleven cases or 65 per cent. Many of these strains were subcultured successfully and carried along for several generations. The organism was recovered from brains of rabbits injected with virus of these nasal washings in five instances as well as from the brains of rabbits injected with the organisms from these nasal washings

FIG. 13. Rabbit brain. Cortex of cerebrum showing focal infiltration with round cells in proximity to vessel showing mononuclear cell infiltration of the adventitia. Rabbit injected with same inoculum as animal pictured in Figs. 11 and 12.

FIG. 14. Rabbit brain. Mononuclear cell infiltration of the parenchyma and of the adventitia of vessels in the basilar ganglia. Animal injected with Berkefeld filtrate derived from nasopharyngeal mucous membrane of animal pictured in Figs. 11 and 12.

in three instances. Control studies of nasal washings were negative in eight instances (mastoiditis (2), sinusitis, pyelitis, appendicitis, empyema, cholelithiasis, nephrolithiasis).

The organism was recovered from the nasopharyngeal mucous membrane of three rabbits which showed typical clinical and pathological pictures after inoculation with human infectious material.

Cerebrospinal fluids have yielded the organism in ten out of twenty cases. It was found in one case on direct smear of the sediment of the centrifugalized spinal fluid. The organism was recovered from the brains of eight rabbits injected with the spinal fluid itself, and from the brains of four rabbits injected with the organisms derived from these spinal fluids. Eight spinal fluids from patients suffering from brain abscess, brain tumor, psychasthenia, uremia, multiple sclerosis, tuberculous meningitis, neurosyphilis and spinal cord tumor, were all cultured with entirely negative results.

A total of 51 rabbit brains was cultured, using Berkefeld filtrates of brain, blocks of brain and emulsions of brain. The organism was successfully recovered from 34 of the 51 brains cultured, or 66 per cent.

A total of six monkey brains from animals injected with various viruses was cultured with five positive results, or 85 per cent. The organism was demonstrated in cultures of blocks of a glycerolated brain kept in the refrigerator for three and a half months. A positive culture was obtained from the brain of a monkey that was injected with the seventh generation of a culture of human nasopharyngeal mucous membrane.

After numerous attempts and by various means we have finally been able to isolate the organism from human brains. We achieved our earliest and best results with a case of lethargic encephalitis that ran a very rapid course—death ensuing in five days. Positive cultures were obtained on the first attempt by the use of large blocks of brain tissue. In another instance, we were able to use only filtrates because the brain was grossly contaminated. It is our impression that the organism exists in the

FIG. 15. Rabbit brain. Area of mid-brain showing perivascular infiltration. Animal injected with cerebrospinal fluid from human case.

human brain in an attenuated form or in such small numbers that it is only by persistence and the use of special methods, viz., concentration *in vacuo*, that successful growths are obtained.

The seventh generation of a culture, originally derived from a 50 per cent. glycerolated filtrate of human nasopharyngeal mucous membrane, brought down a monkey with the typical clinical and pathological picture. As in the case of the virus, however, monkeys are apparently refractory to this organism.

Our rabbit inoculation experiments have been carried out with a number of strains preferably in the later generations. About 50 per cent. have succumbed with typical lesions. The incubation period varies from 2 to 42 days. The strains used have been two; derived from filtrates of two human nasopharyngeal mucous membranes. Filtrates of cultures from the third to the eleventh generations were injected intracranially into 20 rabbits—12 succumbing with typical lesions. Further successful animal transmissions were made with filtrates of these brains. Cultures derived from the brains of inoculated animals have proved pathogenic for rabbits in approximately 50 per cent. of the rabbits injected.

Colonies picked from solid cultures of these strains have been grown in fluid medium. These cultures injected intracranially into rabbits have produced lesions in five of eight animals.

Cultures of organisms derived from spinal fluids and of organisms isolated from the brains of rabbits injected with these cultures have produced lesions in five of twelve animals inoculated.

We wish to point out in connection with our animal experiments that we have not only produced typical lesions in rabbits with cultures derived from virus of various kinds but have been able in many instances to recover the organism from the brains of animals so injected and to produce again the disease in animals with later generations of these same organisms.

The microorganism which we have isolated resembles in morphology and in cultural characteristics that found by Flexner and Noguchi in poliomyelitis. It differs in virulence, incidence and in the ability to infect rabbits. The isolation of the

organism from the spinal fluid sharply differentiated this disease from poliomyelitis.

References

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2. LOEWE, HIRSHFIELD AND STRAUSS: *Jour. Infect Dis.*, 1919, xxv, 378.
3. LOEWE AND STRAUSS: *Jour. Am. Med. Assn.*, 1919, lxxiii, 1056.

Since our article was read we have noted in the *Comptes Rendu des Sciences de la Societe de Biologie*, March, 1920, articles by Levaditi and P. Harvier confirming our work. They have succeeded in producing encephalitis in rabbits and guinea pigs by the intracranial and intraocular injection of infected human brain. After a number (7) of passages through the rabbit they found that the virus became pathogenic for the monkey. They agree with us that epidemic encephalitis is due to a specific filterable virus different from poliomyelitis; that it can be preserved in glycerin; and that no organism could be obtained by the ordinary methods. They make no mention of an attempt to cultivate their virus on the tissue-ascitic fluid medium.

Discussion:

DR. NORRIS: I want to congratulate Drs. Strauss and Loewe on their notable presentation, and the splendid work which they have done. I think there is no question at all but that they have proved their point, namely, that we are dealing with a filterable virus. I do not feel at all capable of expressing any opinion of the bacteriological work. I have done enough of that work to know how precarious the Noguchi method is, and what care must be used with it. I think as the paper was presented that it would be very ungracious to say that Dr. Loewe has not proved his point, but I think that there is the opening left to me to think that the organism which he has shown on the screen is not the etiological factor, but one which is symbiotic with the filterable virus. That of course is nothing against Dr. Loewe's claim as to the infectivity of his cultures. We must take it for granted that a filterable virus was present in the eleventh generation and that it has been growing in symbiosis with the etiological organism.

DR. WOOD: I have had only three recent autopsies on cases of encephalitis, and what is interesting in the sections of these lesions is their great extent as compared to the human cases. The cortical lesions were very slight in the human brains, although they varied in distribution and in amount, and even in the basal ganglia and pons were less than those shown in the animals.

DR. LIBMAN: In regard to the point Dr. Norris made, I am not sure that it is correct. Even if one assumed that the organism one sees in these cultures is not the agent of the disease, but that the agent is in the fluid part of the culture, the fact would still remain that Dr. Strauss and Dr. Loewe have succeeded in cultivating that virus, and have infected animals with it. The work is of importance also in that it helps prove the validity of the poliomyelitis work. Apparently, we will find that there is a number of

filtrable viruses which show the same organism on microscopic examination. That they do not occur all over is evidenced by the fact that they are not present in the cerebro-spinal fluid in cases of poliomyelitis, but have been recovered from the spinal fluid in cases of epidemic encephalitis. For the present there is the greatest difficulty in deciding the nature of these organisms, except by animal inoculation. For proper classification, we will need new methods. It reminds me of the early work in bacteriology. When bacteriology was first begun, the organisms were grown in fluid media, and pure cultures could not, except by accident, be obtained. Later, solid media were introduced, and still later the brilliant mind of Theobald Smith increased our knowledge of differentiating these bacteria by means of studies in acid production. It seems to me that it is of the greatest importance to have men enter the field of bacteriology who have profound chemical knowledge.

As Dr. Strauss has pointed out, you can use the animal inoculations for differential diagnosis. Last summer I saw a woman who had been subjected to artificial induction of labor, because she was thought to be suffering from toxemia pregnancy. The clinical appearance of the case made me suspect that she was really suffering from epidemic encephalitis. I made washings of the nasopharynx, and they were injected into rabbits by Dr. Loewe. Typical lesions were produced in the animals.

DR. LOEWE: I wish to emphasize the fact that we cultivated the virus in solid media and selected isolated colonies. The colonies were then inoculated in fluid medium, and with such cultures positive results were obtained in animals.

ANEURYSM OF THE HEPATIC AND GASTRODUODENAL ARTERIES, WITH RUPTURE OF THE ANEURYSM INTO THE DUODENUM

HENRY R. MULLER, M.D.

The history in this case is brief, because the man, who was a postman, forty years old, was brought to the hospital one evening "in extremis." The only history which could be obtained was that about one month before, he had vomited a considerable quantity of blood. He had not been well since then, and had complained of weakness and frequent attacks of epigastric pain. Two days before his admission the patient began to have slight fever, it is said, with severe headache and abdominal pain. He vomited a considerable quantity of dark brown fluid which contained some bright red blood. On admission the patient's pulse was exceedingly small; he was cyanosed and very weak. During the night he was extremely restless, and he died about seven o'clock the next morning.

On admission his blood pressure was 105 systolic and 50 diastolic; temperature 100°, pulse 132, respiration 24.

Autopsy: The body was a well-developed and well-nourished male subject. The skin and mucous membranes were remarkably pale. There was no external evidence of syphilis. The bony frame was normal and showed no evidence of syphilis. Since the examination was restricted to the chest and abdomen, a good view of the base of the tongue could not be obtained, but so far as could be seen, there were no scars present. The penis was normal and a definite scar could not be made out. The testicles were larger than normal. Superficial lymph-nodes were not palpable, excepting in both groins, where they were slightly enlarged and indurated.

The *heart* was moderately enlarged, due to an hypertrophy of the left ventricle. The musculature showed no focal lesions except large opaque areas of degeneration in the tips of the papillary muscles in the left ventricle. Both coronaries showed early arteriosclerotic lesions and a few very doubtful lesions of syphilis were present in the upper thoracic and lower abdominal portions of the aorta.

The *lungs* were soft and fluffy, and showed a high grade of anemia. There were no focal lesions. The pulmonary vessels were normal and a search for syphilitic lesions yielded negative results.

The *spleen, adrenals* and *pancreas* were negative.

The *kidneys* appeared slightly larger than normal, their combined weight being 325 gm. The capsule was somewhat adherent. The cortex was slightly thickened, and the markings were indistinct, due largely to a high grade of anemia.

The *pelvis, ureters, bladder, seminal vesicles* and *prostate* presented nothing unusual.

The *liver*, pale yellow in color, presented no focal lesions. The bile ducts were patulous.

Of the *gastrointestinal tract*, the esophagus was normal. The stomach contained about one liter of blood-stained watery fluid. The mucosa of the duodenum was edematous, and a small circular ulcer, measuring 3 mm. across, was found on the posterior wall about 3 cm. from the pyloric ring. Behind the duodenum at this point was found an irregularly egg-shaped mass about 2 x 5 cm. The cavity in this mass communicated with the duodenum through the ulcer referred to above, and upon dissection proved to be an aneurysm of the hepatic branch of the celiac axis, involving also the gastroduodenal branch arising from the hepatic artery. The sac was lined with laminated blood clots.

The remainder of the gastrointestinal tract presented nothing unusual apart from a hyperplasia of the solitary follicles of the colon, and the presence of a large amount of altered blood, particularly in the large gut and the lower ileum.

Microscopic Examination: Sections of the wall of the aneurysm showed practically an entire absence of elastic tissue fibers, the wall of the sac being made up almost completely of hyalin connective tissue. One section showed a small calcified plaque in the wall, and focal collections of lymphocytes around the blood vessels of the adventitia, and small collections of lymphocytes and large brownish pigment-bearing cells in the wall of the sac.

A section through one of the slight scar-like depressions of the aorta, suspicious of being syphilitic in the gross, showed no loss of elastic fibers nor any other signs of syphilis. There was only thickening and atheroma of the intima.

Sections of the wall of the aneurysm stained by Levaditi's method for spirochetes failed to show any such organisms.

A CASE OF SARCOMA OF THE LUNG

A. V. ST. GEORGE, M.D.

(From the Pathological Laboratories, Bellevue Hospital, Dr. Douglas Symmers, Director)

Primary tumors of the lung occur so infrequently that every case is well worth reporting. When the tumor is a primary sarcoma, it comes almost into the category of medical curiosities. Adler (1) was able to find only ninety cases in the literature, but many of these lack sufficient evidence to make his report entirely trustworthy. A case was reported in the *Medical Clinics of North America* (2), but the description is not quite clear as to the origin of the tumor. One or two other cases have been reported in this country during the past three years.

The patient was a man, age 52, who was admitted to Bellevue Hospital on the service of Dr. Nammack, whom I desire to thank for permission to abstract this case, on December 9th. He died December 26, 1919. The patient stated that he had a cough every winter for many years and expectorated a great deal during these periods. He had been feeling bad for a week, but did not stop work until three days previous to admission. He was suffering from extreme shortness of breath, was very weak and his temperature was high.

Physical examination showed a poorly nourished white male. The pupils were equal, reacted to light; no nystagmus; the scleræ were clear and the conjunctivæ normal. The mucous membrane of the mouth was slightly congested, the tongue covered and dry, and the tonsils slightly enlarged. There was no rigidity of the neck; the anterior and posterior cervicals were enlarged. The heart was displaced to the right of the mid-sternal line. Lungs showed flatness on left side from second interspace downward, anteriorly, and extending into the axilla as high as the second rib, and as far back as the mid-axillary line. Over this the vocal fremitus was absent. The dullness also extended to the posterior axillary line in the fifth interspace. The rest of the physical examination was negative.

December 13, 1919 (note by Dr. Nammack): The patient looked chronically ill, markedly emaciated, anemic and very irritable. The heart was displaced to the right so that the right border was two and a half inches to the right of the mid-sternal line. The apex seemed to be under the lower part of the sternum. The maximum impulse was in the fifth space, one inch to the right of the mid-sternal line. The left border of the heart could not be elicited. A systolic murmur was heard all over the right chest anteriorly. Over the second space on the left side there was a short to-and-fro murmur, probably pleuro-pericardial. The right lung was resonant all over and there were harsh vesicular breath sounds. The left lung was resonant in the posterior and anterior portions, from the apex to the second space. The breath sounds on this side also were harsh and vesicular. A few subcrepitant râles were heard at the base, anteriorly, from the second space down, and as far back as the posterior axillary line there was absolute flatness and absence of breath sounds. The veins of the abdomen were distended. The patient held himself rigid so that he could not be examined satisfactorily. The axillary, epitrochlear and inguinal lymph nodes were slightly enlarged. The knee jerk reflexes were hyperactive. Blood pressure: Right—95/45; left—95/50. Impression: Tumor of lung (primary), possibly Hodgkin's disease. The patient was running septic temperature.

December 16, 1919: Blood Wasserman negative.

December 18, 1919: Patient was running septic temperature with one or two chills every day. Blood culture was positive for *streptococcus viridans*.

December 20, 1919: Exploratory thoracentesis showed no fluid. Rectal examination was negative except for prostate being somewhat firm.

December 23, 1919: Roentgen-ray examination. The left pulmonic field was very small, due to complete obliteration of the illumination of the lower three fourths. The upper boundary of this area of illumination was convex and located at about the level of the second rib anteriorly. The lower boundary was located at the tenth rib posteriorly. There was obliteration of the illumination of the left costophrenic sinus. There was a small illuminated area between the left costophrenic sinus and the lower portion of the non-illuminated area. There was retraction of the trachea into the left thorax, and slight deviation of the heart to the right. The findings suggested the presence of a mass in the left lung associated with small pleural effusion. Diagnosis: Tumor of the lung.

The relatively sudden onset of the symptoms and the rapidly fatal course of the disease was of clinical interest in this case, and was also noted in several of the other cases reported. In this instance, the *streptococcus viridans* sepsis undoubtedly influenced the rapid termination.

Postmortem Record: The body was that of a white male, 52 years old, five feet, ten inches in height and weighing about 125 pounds. The external configuration of the body was normal, except for a marked generalized

icterus and a small recent decubitus over the sacrum. Rigor mortis was complete. Postmortem hypostasis was present in the dependent portions of the body. The hair everywhere was normally developed and distributed. The lymph nodes in the left axilla were palpable. The scalp was clean and covered with gray hair. The pupils were equal, regular and in mid-dilatation. The scleræ were icteric. There was one petechial spot in the lower conjunctiva of the right eye. The nose and ears externally were negative. The teeth were in fairly good condition. The lips were dry and excoriated. The thorax was symmetrical. The abdomen was not prominent. The external genitalia were negative. There was a pendulous fibroma, about the size of a pigeon's egg, on the posterior aspect of the right thigh. The subcutaneous fat was poorly developed. The abdomen was dry and there were no adhesions. The liver extended 17 cm. below the free costal margin in the mid-axillary line. The diaphragm reached the seventh rib on the right, the fifth space on the left. The appendix was small and thickened and bound down by numerous adhesions to the posterior wall of the abdomen.

Chest: On opening the thoracic cavity, the heart was displaced to the right and downward so that fully 8 cm. of the precordial area was to the right of the median line. The thymus was not recognizable as glandular tissue and was replaced by numerous fibrous adhesions between the lungs, mediastinum and the precordial area. The left pleural cavity was practically obliterated by many firm and some easily destroyed adhesions throughout the entire extent except near the apex. The cavity contained approximately 20 c.c. of fluid. The right pleural cavity contained similar adhesions which were easily destroyed. The pericardial sac contained about 40 c.c. of yellowish purulent fluid. The visceral and parietal portions of the pericardium had a dull, reddish, glazed appearance on which there was some fibrinous deposit.

Heart: The heart was large, weighing 400 gm. The epicardium was of a dull red color as described. The muscle in the left heart was hypertrophied. On section, it was fairly firm, reddish brown in color, and there were numerous fine whitish striations, some of them very prominent. The endocardium was smooth but opaque in the left auricle and somewhat opaque in the left ventricle. The valves on the right side were normal. The foramen ovale was patent. The mitral valve was somewhat thickened, likewise the chordæ tendinæ, and there was slight retraction of their margins. On the aortic valves there were vegetations especially on the right posterior cusp where a large vegetation, roughly 75 x 100 mm., projected upward into the aorta. On the remainder of the cusps there were small verrucous vegetations. The cusps were fused for a distance of from 3 to 4 mm. Immediately behind the aortic valve there were hard, calcific atheromatous changes. The coronary vessels showed a few soft atheromata. The aorta showed atheromatous changes throughout its entire extent, more marked in the lowermost portion where there were calcific plaques. The pulmonary artery was normal.

Lungs: The left lung weighed 2285 gm. The lower lobe was most prominent and of a stony hardness. Its position in the thorax caused it to compress the upper lobe considerably so that this portion of the lung was soft and practically without air. At the apex there were a few small, calcific

nodules. The lower lobe was everywhere covered by dense fibrous adhesions and connective tissue. On section, the entire lobe was converted into a stony-hard, white tumor mass in which no definite structure could be ascertained except here and there localized areas which had a distinctly yellowish tinge

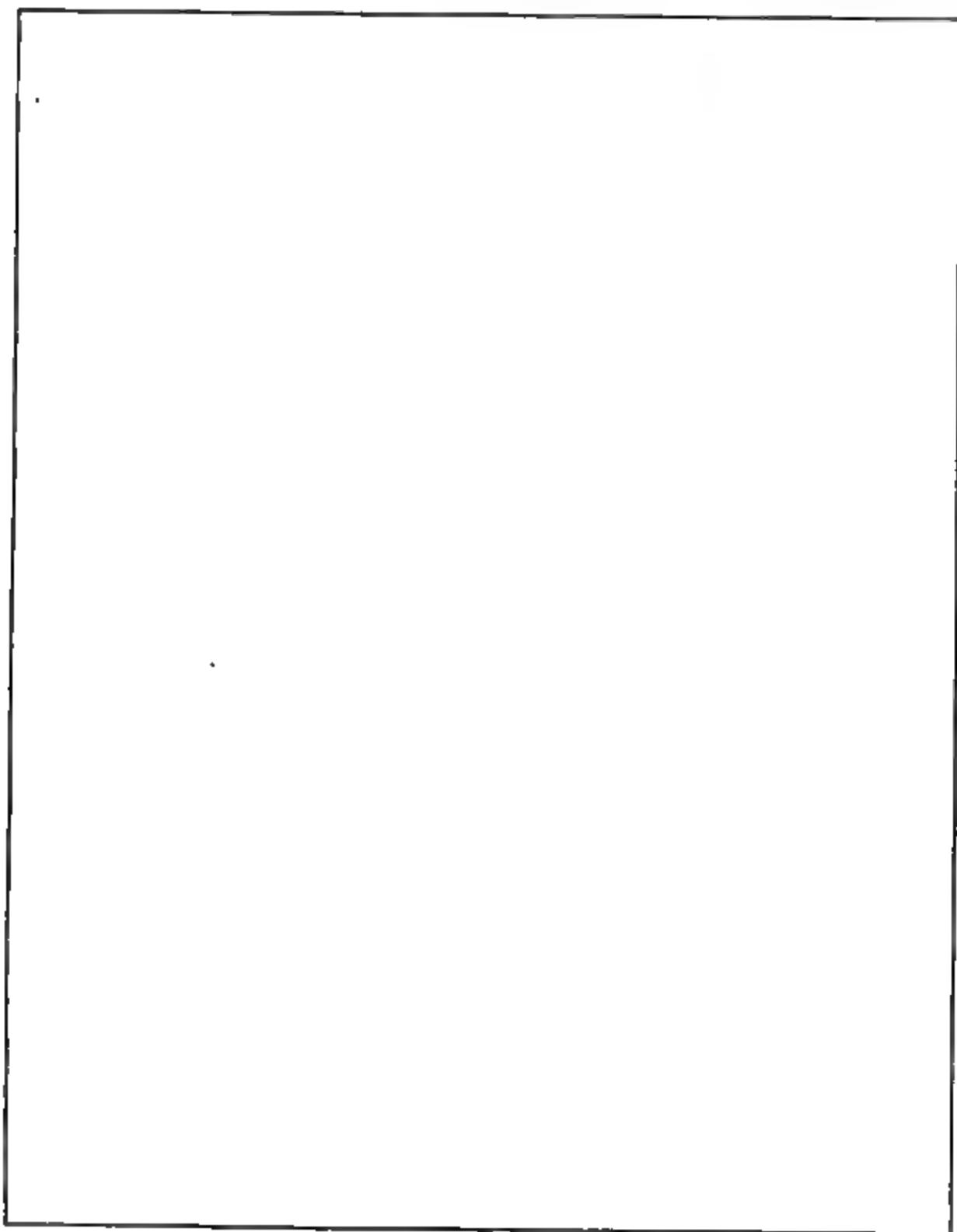


FIG. 1. Two cross sections of lung, showing primary sarcoma.

(Fig. 1). A few small, caseous areas were also present in this situation. The tumor mass resembled carcinoma, was very firm and not markedly vascular. The bronchi on this side were considerably congested and compressed, but contained no fluid. The peribronchial lymph nodes were not enlarged.

There was no definite point of origin of this tumor. The smaller bronchi in this lung were for the most part obliterated; the larger branches were dry and glazed.

The right lung was large and crepitated throughout. In the lower portion it was of a darker red color and firmer. On section and on palpation, there were a number of hard, circumscribed nodules which, on opening, were of a dull red color, somewhat paler in the center, the largest measuring not more than one and one half cm. in diameter, and the majority about the size of a pea. The lower lobe exuded a considerable amount of dark reddish, frothy blood. At the apex were two or three calcific nodules. The bronchi on the right side were congested and contained a moderate amount of pink, frothy fluid. The peribronchial lymph nodes were not enlarged. The mediastinal area showed no tumor formation.

Spleen: The spleen was large and weighed 655 gm. The capsule was not thickened. The organ was somewhat soft and friable. On section, it presented a dull red, grumous surface in which the lymphoid tissue was no longer distinguishable. There were two small accessory spleens in the mesentery near the lower pole. The splenic artery showed a few yellowish atheromata.

Liver: The liver was normal in size; the surface and border were smooth, and the organ was somewhat compressed in its antero-posterior diameter. On section, it presented a dull grayish color and exuded a slight amount of blood. There were no other lesions in the gross. The duct and vessels were patent. The gall-bladder wall was normal. The gall-bladder was distended with a considerable amount of dark green, sticky bile.

Pancreas: The pancreas was normal in size and normal on section. The lymph nodes at the head of the pancreas and in the region of the gall ducts were enlarged, pink in color and succulent, but without evidence of tumor growth.

Adrenals: The adrenals were normal in size. On section, they exuded a considerable amount of blood. Both adrenals contained whitish, irregular but sharply demarcated areas which were adenomata.

Kidneys: The kidneys were normal in size and imbedded in but little fat. The capsule stripped without much resistance, leaving a finely granular surface in which there were numerous whitish areas about 1 to 2 mm. in diameter (adenomata). On section, the cortex was somewhat narrowed and a considerable amount of fibrous tissue was present. In the cortex of the left kidney near the upper pole was a pale, somewhat oval shaped, sharply demarcated area, about 5 mm. in diameter, 1 to 1.5 cm. in length, and apparently a tumor metastasis. The pelvis and ureter of both kidneys were normal.

Bladder: The bladder was distended with about six ounces of clear urine, but there were no lesions in the gross.

Testes: The testes were normal in size and rather firm. The tubules pulled out readily.

Prostate: The prostate was normal in size. On section, it showed a very firm, somewhat cream colored, smooth surface.

Esophagus: From its commencement to its termination in the stomach, it was normal.

Stomach: The stomach showed no marked lesions except slight congestion. The rugæ were prominent.

Intestines: The remainder of the large and small intestines showed no lesions in the gross.

Appendix: The appendix was much thickened and sclerotic and its lumen was considerably narrowed.

Tongue: The tongue was normal, as were also the larynx and trachea.

Thyroid: The thyroid was normal in the gross.

Brain: The scalp was removed without difficulty. The skull sawed through readily. On removing the calvarium, a considerable amount of pial fluid exuded from the cranial cavity and also considerable fluid was found in the pial tissue. Throughout the pia, especially on the convex surfaces of the cerebral lobes, there were irregular ecchymotic areas. The vessels at the base showed atheromatous changes. On section, the brain was otherwise normal.

Examination of the vertebræ and the pelvic bones, the head of the femur and the humerus, and some of the ribs showed no changes in the gross.

Note: Cultures from the spleen, at autopsy, showed *Streptococcus viridans*.

Anatomical Diagnosis:

Heart: Purulent pericarditis. Fibrous myocarditis, vegetative aortic endocarditis. Chronic mitral and aortic valvulitis. Patent foramen ovale.

Aorta: Atheroma.

Lungs: Apical tuberculosis, healed. Chronic adhesive pleuritis. Tumor of left lung with metastasis in right lung. Pulmonary congestion. Acute bronchitis.

Spleen: Acute splenic tumor. Accessory spleen.

Liver: Chronic passive congestion.

Kidneys: Chronic nephritis. Tumor metastasis. Adenomata.

Adrenals: Congestion. Adenomata.

Prostate: Adenomatous hyperplasia.

Appendix: Chronic appendicitis.

Brain: Pial œdema. Sclerosis of basal vessels.

General: Arterio-sclerosis. Icterus. Septicæmia, *Streptococcus viridans*.

Microscopic Examination: Microscopically, the primary tumor and the metastases in the right lung showed large, round sarcoma cells with a distinct perivascular and alveolar arrangement, forming the so-called alveolar sarcoma of the lung, similar cases of which have been described by Adami, McDonnell and others. Microscopic sections of the other tissues showed nothing remarkable. The metastatic foci everywhere had the same histological characteristics as the original tumor.

It is appreciated that the lesion primary sarcoma of the lung has often been questioned for many good and valid reasons. On the other hand, after as complete a search as we were able or permitted to make, no other site of origin was found. In this

individual, as in other reported cases, the nature of the tissue from which the tumor sprang remains obscure.

References

1. ISAAC ADLER: *Primary Malignant Growths of the Lungs and Bronchi*, Longmans, Green & Co., New York, 1912.
2. *Medical Clinics of North America*, Vol. 2, p. 1145.

Discussion:

DR. PAPPENHEIMER: We have recently had two cases of mediastinal sarcoma at the Presbyterian Hospital, occurring within a few days of each other. In both of these the lung was extensively involved, and may have been the primary site of the tumor. They differed from Dr. St. George's case in the more extensive involvement of the mediastinal lymph nodes, and the possibility of their being lymphosarcomata was of course obvious. Histologically, however, neither of these tumors has the appearance of the ordinary lymphosarcoma, the cells being much larger in size and more polymorphous than is usual in lymphosarcoma. One of these tumors involved the upper part of the lung; the other grew from the hilus along the peribronchial and perivascular tissue, causing great thickening of the bronchi and blood vessels.

A CASE OF ACUTE YELLOW ATROPHY, WITH COMPENSATORY CHANGES IN THE LIVER

ELI MOSCHCOWITZ, M.D.

Cases of acute yellow atrophy are not so infrequent that they need be reported, but this specimen reveals some unusual and instructive features.

The patient was a woman 54 years old, admitted to Beth Israel Hospital on November 12. She gave a history of jaundice for nine months. A day or two before her admission to the hospital the jaundice increased, and increased progressively until her death four days later. The only other symptoms were weakness and epigastric distress. During the nine months previous to admission she was able to do her own work. She was irrational during her stay in the hospital. She became comatose toward the end.

Examination of the urine showed much albumin, casts, but no leucin or tyrosin. The Wassermann reaction was negative. The diagnosis of acute yellow atrophy was made by Dr. Barsky ante-mortem. The liver weighed 620 gm. (formalin). Unfortunately the organs showed considerable post-mortem necrosis. The capsule was wrinkled. On section the color was

ochre red, scattered in which and lying close together were numerous irregular islets of yellow liver tissue. Microscopically, the ochre colored areas represented a fairly firm growth of new fibrillar connective tissue, which contained many round cells, remains of the capsules of Glisson, deeply bile stained epithelial cells and a large number of newly formed bile ducts. The yellow areas were islets of liver trabeculæ. These were well preserved, but the normal morphological unit structure of the liver lobule was absent. There was no central vein. The trabeculæ, especially in the central portion of these nodes, were broad, and contained sometimes three or more layers of cells. The nuclei were polymorphous and varied greatly in size and shape. An occasional mitotic figure may be seen.

These nodules may be interpreted as efforts on the part of the liver to compensate for the destruction of the liver parenchyma.

The first interesting feature is the unusually long history of duration of the illness. This is borne out in a measure by the histological changes in the organ. The large amount of new connective tissue can reasonably be interpreted as representing a duration of weeks or months rather than days.

The second interesting feature is the evidence of regeneration. This is shown not only in the development of new bile ducts but in hyperplasia of the liver trabeculæ. This liver represents, apparently, a stage just preceding that known as "nodular hyperplasia" of the liver.

Discussion:

DR. JOBLING: I should like to ask Dr. Moschcowitz if there was a history of any kind of intoxication, and also what was the occupation of the patient.

DR. MOSCHCOWITZ: There was apparently no history of intoxication of any kind. The patient was a housewife.

DR. JOBLING: Had she been doing any sort of war work?

DR. MOSCHCOWITZ: No, she lived on the East Side, and looked after her family, doing washing, etc. This case has made me wonder whether acute yellow atrophy is not really due to a progressive intoxication.

DR. JOBLING: What were the blood findings?

DR. MOSCHCOWITZ: I think that the blood was not examined.

PATHOLOGICAL FINDINGS IN SEVENTEEN CASES
OF PNEUMONIA DURING THE INFLUENZA
EPIDEMIC OF JANUARY-FEBRUARY, 1920

HENRY E. MELENEY, M.D., AND ALWIN M. PAPPENHEIMER, M.D.

The following is a summary of the pathological findings in the seventeen cases of pneumonia which came to autopsy at the Presbyterian Hospital, New York, between January 10 and February 7, 1920. The ages ranged between 20 and 70 years. There were eight males and nine females. The duration of the disease varied from 4 to 24 days, only three, however, being over 10 days in duration. Eight gave signs clinically interpreted as lobar consolidation. The other nine cases were described clinically as having bronchopneumonia or no definite signs of consolidation. Of 13 cases on which a leucocyte count was done, eight had 15,000 or more, one had 9,000, and four had less than 6,000. In the cases having a leucocytosis the pneumococcus was usually found to be the predominating organism at autopsy. The cases with a leucopenia all showed either no pneumococcus or a pneumococcus together with *B. influenza*.

At autopsy the cases presented a great variation in extent and type of lung involvement. In half the cases all five lobes were involved and in all these the confluent lobular type of pneumonia, usually associated with hemorrhagic edema, was the dominating picture. Three other cases each had four lobes involved and in two of these the confluent lobular type of consolidation predominated. In cases where only one lobe was involved consolidation was usually only of the lobar type. One case, associated with hemolytic streptococcus empyema, showed no consolidation.

All except one case of the series showed a pleurisy at autopsy. In one half of the cases one or both chest cavities contained purulent fluid. Usually this was not over 100 or 200 c.c. in amount. In two cases there had been great accumulation of pus, and on one of these a thoracotomy had been performed. Extensive empyema, then, cannot be considered a very prominent complication

in this series. The only definite pulmonary abscess found in the whole series was in the unoperated case of empyema. The abscess was subpleural and on culture showed hemolytic streptococci and *B. influenzae*. Bronchiectases were found grossly in three cases, and all of these were old lesions, judging by their microscopic appearance. In several other cases, however, microscopic examination showed small acute bronchiectases.

The gross and microscopic lesions of the various portions of the respiratory tract may be summarized as follows:

Larynx: This was examined in ten cases. It was usually normal or slightly congested. It showed ulceration in one case and slight edema in two cases.

Trachea and Primary Bronchi: These showed congestion in every case, varying from a mild degree to a very intense hemorrhagic condition which was present in about a third of the cases. There was gross ulceration only in one case. Microscopically most of the cases showed loss of epithelium with edema of the basement membrane, of the submucosa and of the peritracheal tissue.

Small Bronchi: A purulent or fibrino-purulent bronchitis was found in practically all cases. Three cases showed marked regeneration and metaplasia of the bronchial epithelium. These cases were all pneumonias (pleural) primarily of the influenza type. The rapidity with which metaplasia may take place is shown by the fact that in one of these cases the duration of the disease was only four days.

Infundibula and Alveoli: The exudate here varied not only in different cases but in different portions of the same lobe. There were patches of frank hemorrhage in about two thirds of the cases, and in all these the confluent lobular type of pneumonia was predominant. Fibrin was rather less in amount than is usually seen in lobar pneumonia, but in this series the amount of fibrin seems to bear little or no relation to the type of pneumonia present. Most of the cases showed many polymorphonuclear leucocytes in the alveolar exudate, and it is interesting to note that in almost every instance where there was leucocytosis dur-

ing life the alveolar exudate at autopsy contained many pus cells. In cases with no clinical leucocytosis, however, the alveolar exudate contained either few cells, or else those present were mostly mononuclears. Only two cases were exceptions to this rule. There was marked edema of the lungs in about two thirds of the cases, occurring mostly, of course, in the unconsolidated portions of the lungs. Changes in the alveolar walls were in general not extensive, except for extreme congestion which occurred in the large majority of cases. Hyaline necrosis of alveolar walls, so often described in influenza pneumonia, was present in but three cases, and was extensive in only one case, that which was in every other way the most typical case of influenza pneumonia in the series. Interstitial inflammation of the lung tissue was not marked in any case.

Blood Vessels: Thrombosis of the vessels of the lung was never noted grossly, but was found microscopically in four cases. There was no associated lesion of the vessel wall in these cases, but in three other cases focal infectious lesions of vessels were found, characterized by necrosis and infiltration with leucocytes. These vessels showed no thrombosis although the intima in places showed swelling and edema. This is an interesting lesion which deserves further study in cases of pneumonia associated with influenza.

Bacteriology: During life, blood cultures were made on seven cases. Six of these were sterile, the other one showing pneumococcus Type 1. Sputum examinations by mouse inoculation were done on nine cases, showing a pneumococcus in eight cases and a non-hemolytic streptococcus in one case. At autopsy cultures were made on about half of the cases from the lungs, small bronchi and trachea. In the lungs 75 per cent. of the cases cultured gave a pneumococcus, or else *B. influenza* with either a pneumococcus or a staphylococcus. From the small bronchi and trachea, cultures were usually identical, and were never pure cultures of a single organism. The striking point is, however, that *B. influenza* was the only organism which was found in these localities in every case cultured. Microscopic sections of

all lungs, and wherever possible of trachea and primary bronchi also, were stained with Gram-Weigert stain for bacteria, using saffranin as a counter stain. Seventy-five per cent. of the sections of trachea or large bronchi showed organisms. When present they were always on the surface of the mucosa. Gram-positive cocci were always present, and in addition two showed Gram-negative bacilli morphologically similar to *B. influenzae*. Besides those found on the surface, two cases showed Gram-positive diplococci and one case *B. influenzae* in the submucosa and in the peribronchial areolar tissue. In one case the peribronchial lymphatics were distended with fluid containing pus cells and many Gram-positive diplococci, many of which were disintegrating, and most of which were intracellular. This was the only case in which any involvement of peritracheal or peribronchial lymphatics was seen microscopically. Winternitz¹ has recently demonstrated by injection of india ink and bacterial suspensions beneath the mucosa at the upper end of the trachea that there is a very rich network of lymphatics in the submucosa of the trachea which anastomoses freely at the hilus of the lung with the peribronchial lymphatics. With this in mind we searched particularly for evidence of extension of the bacterial infection by way of these lymphatics, but our observations in this small series of cases do not support this idea. In the small bronchi fifteen of the seventeen cases showed organisms in section. Gram-positive cocci were present in every case. One case showed in addition organisms of the typical morphology of *B. influenzae*. In no case were the organisms found in the wall of a bronchus or in the peribronchial lymphatics.

In the lung itself bacteria were demonstrated microscopically in the alveolar exudate in eleven of the seventeen cases. In all of these Gram-positive cocci were present, and in addition two cases showed Gram-negative bacilli morphologically typical of *B. influenzae*, one showed a Gram-positive bacillus and one a Gram-negative diplococcus. In six cases no organisms could be demonstrated microscopically in the alveoli. These were all

¹ Personal communication.

cases from which *B. influenza*, with or without other organisms, had been cultured at autopsy from lungs or bronchi.

Summary

Without attempting to draw any sweeping conclusions from such a small number of cases, certain points seem sufficiently definite to mention.

1. Our cases seem to fall into four groups:

(a) Cases identical with those of the pandemic of 1918 (2 cases).

(b) Cases with some of the features of influenza pneumonia, but showing also a consolidation tending toward the lobar type (10 cases).

(c) Cases of lobar pneumonia identical with those occurring independently of the influenza epidemic (3 cases).

(d) Cases of marked involvement of the pleura, associated with the hemolytic streptococcus, with or without consolidation (2 cases).

2. In general we found a fairly close correspondence between cultural bacteriological findings and organisms demonstrated in sections. *B. influenza*, however, was found much more often culturally than in sections.

3. There was an interesting correspondence between the white blood count during life and the composition of the alveolar exudate microscopically.

Discussion:

DR. PAPPENHEIMER: I think in spite of the small number of cases it is quite clear that there is a much greater diversity in the general run of cases than in last year's pandemic. Dr. Symmers has published a paper which I presume most of you have seen, calling attention also to some of these differences in type. Dr. Symmers emphasizes two points, especially: one, the greater frequency of suppurative pleurisy in this year's cases as compared with the last epidemic, and secondly, the very frequent occurrence of suppurative focal lesions in the lung associated with pleurisy. Abscess was found in only one of our cases, but there was a higher proportion of pleural involvement than in last year's epidemic. Some of the cases were frank lobar pneumonias not different from those of previous years, and we had the impression that many of the cases showed many of the features characteristic of influenza, but complicated by a secondary typical lobar pneumonia.

DR. MACNEAL: Were the cranial sinuses examined in these cases?

DR. MELENEY: The head was not examined in all the cases, but it was examined in about half of them. In four instances there was an acute sphenoidal sinusitis. Occasionally there was congestion of the ethmoidal sinuses, but in no cases were the frontal sinuses, the maxillary sinuses or the middle ears involved.

DR. MACNEAL: Did you make cultures from the sphenoidal sinuses?

DR. MELENEY: Yes, and they corresponded fairly well with what was found in the bronchi. The influenza bacillus, pneumococcus, particularly of type IV, and occasionally other pneumococci, were recovered. There were usually at least two or three types of organisms in the sinuses, and the question was raised at the time by Dr. Humphreys, who was doing the culturing, whether, particularly in the sphenoidal sinuses, there was a possibility that it might be just a terminal involvement.

DR. CECIL: In experimental influenzal pneumonia in monkeys we found the sinuses in a large number of cases and usually the antrum, and very frequently both sides, filled with pus, and we recovered the influenza bacillus from the sinuses. Our cultures were not always pure. In some cases they were mixed with other common bacteria of the nose and throat.

DR. WHEELER: I would like to inquire the methods used in isolating the influenza bacillus, and also the methods for staining it in sections.

DR. MELENEY: The isolation of the organisms at autopsy was done by Dr. Humphreys, and I am pretty sure that he used as a criterion of the influenza bacillus a Gram-negative bacillus of a definite morphology which was hemoglobinophilic. I think he used sodium oleate plates, but these were simply to inhibit other organisms, rather than to identify the bacillus itself. In the section we used a modification of the Gram-Weigert stain, using safranin as a counterstain, which differentiates quite beautifully.

DR. KLINE: Were there any discrete peribronchial lesions observed in the present epidemic??

DR. MELENEY: In making out our summary that was one point that we particularly looked for, and there was not a single case of purely peribronchial pneumonia. They were all either lobar, or what I believe you call confluent lobular, or hemorrhagic lesions.

DR. ROHDENBURG: I would like to say that I was much surprised last fall when reading a series of medical lectures given by Graves (famous because of his description of exophthalmic goiter), and published in America in 1815, by Graves and Gebhardt, to see that he described an epidemic occurring in Dublin. He stated that influenza has been common for some two hundred years. His description of the gross pathology in three successive years, the ordinary mild grippe, the severe pandemic form as observed last year, and the variation from the pandemic form as observed this year, might easily have been written in the present year, with the addition of the label "from such and such a laboratory." It is "up to the minute" except for the bacteriology.

THE PATHOLOGY OF EXPERIMENTAL
PNEUMONIA¹

RUSSELL L. CECIL, M.D.

The experiments described to-night were carried out on monkeys at the Army Medical School in collaboration with Dr. Francis Blake. The primary problem was to differentiate the pathology of the various types of pneumonia, that is, of pneumococcus, streptococcus, and bacillus influenzae pneumonia. At least two, and sometimes all three of these organisms were often found associated in the pneumonias seen in the Army, especially during the influenza epidemic. It therefore seemed very desirable to clear up some of the problems in the pathology of the disease by trying to produce lesions with the organisms in pure culture experimentally. The method of inoculating the monkeys was to inject the bacteria directly into the trachea with a hypodermic syringe, the neck having been shaved and painted with iodine.

The pneumococcus strain used in most of the experiments was a pneumococcus type 1. The streptococcus was a strain of highly virulent streptococcus hemolyticus, while the influenza bacillus was a strain isolated from a fatal case of influenza. Its virulence for monkeys was increased by passage through other monkeys. The dosage used with the pneumococcus was small, a lobar pneumonia similar in every respect to lobar pneumonia in man being produced by doses as small as one-millionth c.c. of a broth culture. Increasing the dosage induced a type of infection in which the disease ran a more rapid course and death usually occurred. A dose of one-thousandth c.c. of pneumococcus type 1 always killed. With the *streptococcus hemolyticus* much larger doses than those used with pneumococci were necessary in order to produce fatal results. Apparently the invasive power of the streptococcus was not as great for monkeys as was that

¹ For a more complete discussion of this see Cecil, Russell L., and Blake, Francis G.: *Jour. Exper. Med.*, 1920, xxxi, 403, 445.

of the pneumococcus, and it was only after we had reduced the resistance of the monkey by "gassing" that we rendered the animals susceptible to the streptococcus.

In the experimental pneumococcus pneumonia of monkeys there is massive consolidation of entire lobes, similar in all respects to that observed in human lobar pneumonia, and microscopical sections show the alveoli filled with leucocytes and fibrin. Monkeys killed in the early stage of pneumonia showed the consolidation to take place about the root of the lung; that is, infection seemed to start about the larger vessels at the root and then spread throughout the rest of the lobe. This idea may not be accepted by all pathologists. Dr. Howard Mason once showed that pneumonia in children often appeared to start at the periphery of the lobe. In our experiments on monkeys however we have never been able to demonstrate an infection beginning at the periphery of the lobe. Microscopical examination shows that the pneumococcus spreads through the alveolar walls by way of the lymphatics, and the bacteria can be demonstrated in the tissues before any cellular reaction has occurred in the alveolus.

In monkeys with experimental streptococcus pneumonia the histogenesis is similar to that of pneumococcus pneumonia, but the cellular reaction is different. Engorgement and hemorrhage are more marked and small abscesses are frequently seen. Pneumonia of this type is usually complicated by empyema.

In experimental influenza and *B. influenzae* pneumonia we have an entirely different set of lesions. Starting with acute rhinitis and sinusitis, the infection travels downward, producing first a tracheo-bronchitis and then in many cases extending on down into the lung, exciting a bronchiolitis, peribronchiolitis and broncho pneumonia. Pus is found in the bronchioles; there is infiltration of leucocytes about the bronchioles and cellular exudate in the adjacent alveolar walls. A few leucocytes are also found in the alveoli, but the latter more frequently contain serum and blood. There is engorgement and hemorrhage everywhere. The influenza bacilli are found chiefly in the bronchioles. In the latter stages of the disease emphysema and bronchiectasis

can be demonstrated. The picture, in brief, is that of *B. influenzae* pneumonia in man. Hyperplasia of the thymus was an almost constant finding with the *B. influenzae* pneumonias. We interpreted this phenomenon as part of a general lymphatic hyperplasia of the cervical and thoracic lymph glands.

Discussion:

DR. KLINE: Did the lungs in the cases of pneumococcus pneumonia show any edema?

DR. CECIL: They nearly always showed some. In the gray stage the lungs were not edematous, but in the early stages of engorgement and red hepaticization they were quite edematous.

DR. PAPPENHEIMER: Were the bronchi free from exudate?

DR. CECIL: They were nearly always filled with exudate.

DR. JOBLING: Did you try to produce the infection by spraying the throats with the cultures?

DR. CECIL: Yes, but without any effect at all with the pneumococcus or streptococcus. If you spray monkeys in the nose and throat with influenza bacilli they get a choryza and bronchitis, but we did not get any such effect with the pneumococcus or hemolytic streptococcus.

DR. PAPPENHEIMER: Were there inflammatory changes associated with the hyperplasia of the thymus?

DR. CECIL: Very little, if any. We found some leucocytes, but it seemed to be mostly a pure hyperplasia. There was not much infiltration; it was simply an enlargement of the entire gland.

DR. KLINE: Did all the monkeys with influenzal pneumonia show a peribronchial lesion, or did some of them show a lobular type?

DR. CECIL: In some there was a confluent lobular pneumonia. We would find areas where there would be a considerable infiltration, but we would never see a whole lobe consolidated.

DR. KLINE: In a series of 154 cases of pneumonia we saw twenty cases in which there was this type just described: a discrete peribronchial and peribronchiolar lesion.

DR. CECIL: It would be interesting to know the bacteriology in those cases.

DR. KLINE: Pneumococcus, *B. influenzae*, *micrococcus catarrhalis*, etc., were found in about the same proportion as in the other types of pneumonia following influenza.

DR. CECIL: The most interesting feature of these experiments has to do with the bacillus influenzae infections. I would like to know just how you gentlemen feel about these lesions—how they compare with what you have seen in human influenza-pneumonia. It is very rare of course to find the influenza bacillus in pure culture in human pneumonia, and therefore it is hard to compare it with the disease in monkeys, but I have studied very carefully the papers by Wolbach and MacCallum, both of whom have described the pathology of pure influenza bacillus pneumonia, and it seems to me that

there is very little difference between their cases and the ones I have shown you to-night. We would naturally have every reason to expect that the injection of influenza bacilli into the lungs of a monkey would produce a type of lesion similar to that observed when this organism is found in man.

DR. KLINE: It is very interesting that Dr. Cecil produced lobar pneumonia in monkeys with one c.c. of culture injected intratracheally. In 1915, in association with Dr. Winternitz, rabbits were injected intratracheally and intrabronchially, and it was found that rabbits that were given five c.c. of pneumococci intratracheally developed no lesion in the lung, but that all animals given pneumococci intrabronchially developed lobar pneumonia. Dr. Winternitz produced lobar pneumonia and I could not, so experiments were done to find out why, and it was discovered that in rabbits there is a remarkable protective mechanism in the bronchi and trachea that gets rid of the pneumococci. Our experiments were carried out with catheters, and I believe Dr. Winternitz thinks that with injection by means of the needle the tissues of the neck are infected when the needle is drawn out, and it is possible that the organisms reach the lung through the lymphatics of the trachea and bronchi. The pictures that were shown on the screen of lobar pneumonia are not those which one sees in experimental pneumonia in rabbits. Such large doses of fluid, usually five, six, or seven c.c. filling the lobe, cause an exudate everywhere and a process more nearly resembling the lobar pneumonia one sees in man. We did not observe the gradual spread. It seems to me that in the pneumonia produced in monkeys by intratracheal injection the lungs show more mottling, that is, the process is more advanced in some portions and less so in others. I think that when the bacteria are introduced intrabronchially the process more nearly resembles that in the human being.

DR. PAPPENHEIMER: We are all interested in this question, and I think that we shall all agree that there are many resemblances between the type of pneumonia Dr. Cecil has produced and the type we have learned to call influenza pneumonia. These resemble each other especially as regards the hemorrhagic character of the lesions, the involvement of the bronchioles, and the tendency to bronchiectasis. There are wanting in Dr. Cecil's preparations certain features which perhaps as Dr. Cecil says may be caused by the admixture of other secondary organisms, but which do not accompany infections with these organisms alone, so that we have come to look upon them as more or less specific for the influenza type. One of these features is the hyaline necrosis of the infundibuli which almost all of the workers have described. Then the majority of Dr. Cecil's lesions has been pretty definitely peribronchial, more the type of pneumonia that MacCallum has described as a sequel to the post-measles pneumonia, and that I think is generally attributed to the *Streptococcus hemolyticus*. The influenza-pneumonias that we saw in human cases were only exceptionally limited to the bronchi. The striking thing about these pneumonias was their very great extent, not as complete consolidation, but as a diffuse hemorrhagic edema, more or less of the pseudo-lobar type. Dr. Cecil has not shown any of the later stages, and I would like to ask him if he has found in the later stages the extensive hyperplasia of epithelium from the bronchi into the neighboring alveoli which seems to be one

of the striking features of the influenza pneumonias. I should like to ask also whether there was a possibility of spreading the infection from the site of inoculation along the deep lymphatics, and whether he studied the trachea of his animals, to determine this point.

DR. CECIL: I was much interested in Dr. Kline's remarks, particularly in regard to infection taking place in the lymphatics about the trachea. I think we controlled that fairly well. We injected a series of three monkeys subcutaneously over the trachea with pneumococci to see if we could produce pneumonia by subcutaneous injection. We were never able to produce pneumonia in a healthy monkey by any method except direct intratracheal injection. We did a contact experiment with some monkeys in a cage, and we were able to produce contact pneumonia. Spraying the nose and throat failed. Subcutaneous and intravenous injections failed to produce any involvement of the lungs. If these monkeys had first had their lungs injured our results might have been different.

In answer to Dr. Pappenheimer's questions, we cut sections of the trachea in nearly all cases, and were never able to see any involvement of the wall of the trachea. In fact, there was usually little inflammation of any kind in the trachea. There was certainly no infiltration of the wall of the trachea, such as we see in human influenza cases, which have almost constantly an acute tracheitis. That is an interesting difference between the influenza infections and the pneumococcus infections. We were looking hard for hyaline necrosis in the alveoli, but we were not successful in finding it. I noticed in sections that Dr. MacCallum sent me that hyaline necrosis was absent in three cases, but it was present in Wolbach's cases. Perhaps I overemphasized the bronchiolitis in our cases, but I think the pictures of the gross specimen are sufficient evidence that we produced a good deal more than a bronchiolitis in these cases. There is an intense edema and hemorrhage, in some cases, especially in the early stages. Another striking thing was the absence of fibrin. We did not get any pleurisy in any of these cases.

CARCINOMA OF THE BRONCHUS WITH THROMBOSIS OF THE SUPERIOR VENA CAVA

RALPH G. STILLMAN, M.D.

(From the Department of Pathology of the New York Hospital)

Carcinoma of the bronchus is not an excessively rare condition but it is sufficiently infrequent to make worth while the mention of the cases that occur. In addition this case which I am presenting has certain features which make it interesting.

The patient was a Russian grave-digger, 38 years old. He was admitted

to the Second Medical Division of the New York Hospital on February 11, 1920, complaining of a swollen throat and spitting of blood.

His family history is negative.

His past history contains little of interest. He had measles in childhood and malaria twelve years before admission. He had been accustomed to several beers and an occasional whiskey and five to six cigarettes daily. He denied venereal infection. He had been subject to chronic cough lasting two or three months at a time but had never had any hemoptysis prior to his present illness. About eighteen months before his admission he began to be a little short of breath on exertion.

His present illness dates from an attack of influenza in March, 1919, eleven months before admission. He had pneumonia at that time and was sick for four months, during which time he was never free from cough and hemoptysis. He went back to work after his recovery but was not free from symptoms and in December, 1919, was forced to stop work. The cough, hemoptysis and dyspnea had grown steadily worse since that time and during the two months before his admission to the hospital were quite severe. He never brought up more than a mouthful of blood at any one time and this was sometimes bright red and sometimes "black."

On admission he was seen to be slightly dyspneic and exhibited well-marked edema of the face, chest and upper extremities. Over the lungs the percussion note was dull throughout. The breath sounds were distinct. There were many sibilant and sonorous râles throughout both chests, with a suggestion of tubular breathing heard at the right of the sternum at the level of the third rib. The reflexes were normal. In the middle third of the right thigh on the postero-external aspect there was a hard mass, about 2 cm. in diameter which felt as if below the fat layer. There were many nodes palpable in the axillæ, some of them measuring as much as 15 to 20 mm. in diameter. The posterior cervical and the inguinal nodes were small but palpable.

His urine showed the presence of a small amount of albumin but no casts. The red cells numbered 3,500,000 and hemoglobin 60 per cent. The white cells were 10,600 and the polynuclears 86 per cent. Two Wassermann reactions were negative. His temperature was normal on admission but rose gradually and varied between 101° and 104° during the last ten days of life. X-ray plates made about ten days before death showed a large mediastinal shadow and signs of infiltration in the right upper lobe. A lymph node was removed from the right axilla but showed only a mild grade of chronic inflammation. He grew progressively worse but was not considered dangerously ill when suddenly one night he had a large hemorrhage from the lung and died.

Autopsy was done on February 26, fourteen hours after death. Only the important findings are given here. The head and arms appeared large in proportion to the rest of the body. There was well-marked edema of the subcutaneous tissues of the head and arms and of the trunk down to the level of the xiphoid cartilage. No edema was apparent below that level. Beneath the skin over the posterior surface of the right thigh was a small

nodule which was very firm and movable, both beneath the skin and on the deeper structures.

The right pleural cavity was dry. The apex of the right lung in its posterior aspect was firmly fixed to the chest wall and was badly torn in the efforts to free it. When the tissue was torn a small amount of dark gray fluid escaped into the pleural cavity. After the removal of the lung, the tissue remaining presented as a thin layer of dark gray tissue whose surface was quite smooth and shining.

The contents of the thoracic cavity were removed *en masse*. The lungs were voluminous, the left was light gray and showed a moderate amount of compensatory emphysema. The right lung presented posteriorly, corresponding to the area of adhesion described above, a ragged cavity measuring about 7 x 9 cm. and situated in the posterior portion of the upper lobe. On opening the trachea it was found to contain a blood clot which filled about one third of its lumen and extended down into the bronchi. The right bronchus, at about 2 cm. from the bifurcation of the trachea, terminated abruptly at the margin of the above-mentioned cavity. This cavity was lined with ragged necrotic tissue and in its walls could be seen the eroded ends of several of the smaller bronchi. There were several blood clots adherent to the wall. One of the branches of the bronchus was opened beyond the cavity and traced down into the lower lobe. The lung in this region was thickly studded with round yellow nodules measuring 3 to 12 mm. in diameter. There was obviously a pneumonia in this portion of the lung but some of these nodules resembled greatly carcinomatous metastases.

At the bifurcation of the trachea was a lymph node about 4.5 cm. in diameter which was largely necrotic. There were several smaller nodes in this region.

The heart was rather small. In the pericardial cavity, at a point corresponding to the reflection of the pericardium and situated nearly at the level of the bifurcation of the trachea, there was a cauliflower-like mass, about 1 x 1.5 x 5 cm. which projected into the pericardial cavity. At one point this mass had grown directly into the lumen of the superior vena cava and appeared there as a small, irregular, firm, pale mass located about 4 cm. above the auricle. Immediately below this mass the lumen of the cava was constricted to a diameter of not more than 4 mm. Above this mass the cava was filled with a thrombus which was pale and firm below but dark red and soft above. This thrombus completely occluded the vessel.

The only metastases found in addition to those in the mediastinal nodes were in the kidneys, each of which contained several nodules of a typical carcinomatous appearance. The nodule in the thigh appeared to be entirely fibrous. The other organs showed nothing noteworthy.

Microscopic examination of the organs showed the lesion to be a carcinoma originating in the bronchus. Section of the right bronchus at the margin of the cavity showed very well the infiltration of the carcinomatous cells beyond the mucosa. The lesion in the lung proved to be a pneumonia with abscess formation. No neoplastic tissue could be found in the lung except in the immediate vicinity of the cavity. The lesions in the kidneys

and the mass in the thigh both proved to be metastatic carcinomas. The tumor was of the cylindrical cell type as could be especially well seen in sections taken from the margin of the cavity in the lung. The greatest interest, perhaps, is found in the study of the metastases in the kidney and the subcutaneous nodules from the thigh. In the kidney, the cells are nearly all flattened or cuboidal and not infrequently resemble greatly the alveolar epithelial cells both in shape and in staining qualities. Further they are at times collected in areas that resemble the alveoli. Some of the cells are collected into whorls that bear some resemblance to pearls but which do not have keratinized centers. From a study of this section alone one would perhaps be justified in concluding that we were dealing here with a tumor having its origin in the alveolar epithelium.

On the other hand the nodule from the thigh shows almost exclusively cylindrical cells resembling those found in the bronchial epithelium and in some places the structure of the bronchus is fairly faithfully reproduced except that none of the cells seem to be ciliated. From a study of this section alone the conclusion would be inevitable that the tumor arose from the bronchial mucosa.

Practically all of the authors who discuss this subject have noted the tendency, especially of the cylindrical cell carcinomas of the bronchus, to show this great variation in the types of the cells, but it is rather interesting to see these two types displayed in two different places in such a striking manner. One may perhaps be permitted to speculate as to whether the consistence of the tissue had anything to do with the morphology of these cells for the squamous cells occurred in the soft tissue of the kidney while the cylindrical cells were found in the firm fibrous tissue of the subcutaneous nodule.

Discussion:

DR. KLINE: At the Montefiore Hospital in the course of over 375 autopsies we have had ten cases of carcinoma of the lung. It is interesting that our last case was very much like the one just presented, except that the tumor arose toward the root of the left lung and extended through the pericardial sac and grew right through the wall of the left auricle. The growth was covered over by an ordinary laminated clot. We have not as yet collected data concerning the nature of the cells making up the tumors, but my impression of the different types is that the most confusing of all, the squamous cell type, might arise from an epithelial growth over cavities formed at some previous time. In going over a number of cases of chronic pulmonary tuberculosis with healed and healing cavities we have seen a down-growth of epithelium, apparently from the bronchial epithelium, over the cavities, that is, lining the cavities. This has been squamous in character,

and we have felt that possibly some of the squamous celled carcinomata of the lung might arise in this way. We have also seen cylindrical cell carcinoma, and in one of the cases the cells were very much like the alveolar epithelial cells. The distribution in this alveolar cell tumor was throughout the body of the lobe, not continuous with the bronchi.

DR. BAEHR: As a further contribution to the study of carcinoma of the lung, I should like to mention an interesting series of coincidences, if they are such, at the Mount Sinai Hospital. Amongst 4,000 autopsies we have three times encountered an association of primary carcinoma of the lung and chronic lymphatic leukemia. The last case occurred about a month ago. In all three cases the primary carcinoma of the lung was accidentally found at the autopsy table. Recently in reciting these experiences to Dr. Gideon Wells he remarked upon the association in mice of carcinoma of the lung and sometimes carcinoma of other organs with a chronic lymphatic leukemia, and his explanation of the association of the two was along the lines of heredity, that is, that the two conditions are sometimes inherited in the same strains.

DR. MOSCHCOWITZ: I should like to ask Dr. Stillman if there was any evidence of dilatation of the superficial vessels.

DR. STILLMAN: No. There was so much edema that the superficial vessels could not be made out.

LOCALIZED CHANGES IN THE HEART MUSCLE AS DETERMINED TO BE IN THE RIGHT BUNDLE BRANCH BY THE ELECTROCARDIOGRAPH

LOUIS FAUGERES BISHOP, A.M., M.D., SC.D., F.A.C.P.

*(Clinical Professor of Heart and Circulatory Diseases, Fordham University
School of Medicine, New York City, Physician to the Lincoln Hospital,
New York)*

The electrocardiograph is an autograph of the heart beat and as such has a large value in bridging the gap which a physician must cross in becoming personally acquainted with the cardiology of his patient. It is like handwriting, the effect of which is very striking in giving an impression of the personality of the writer. So there is a value to the electrocardiograph that is not at present reducible to scientific terms. This represents the extreme and indefinable value of the method. On the other hand, the most striking example of definite, demonstrable, scientific

1 L. H. B. D.

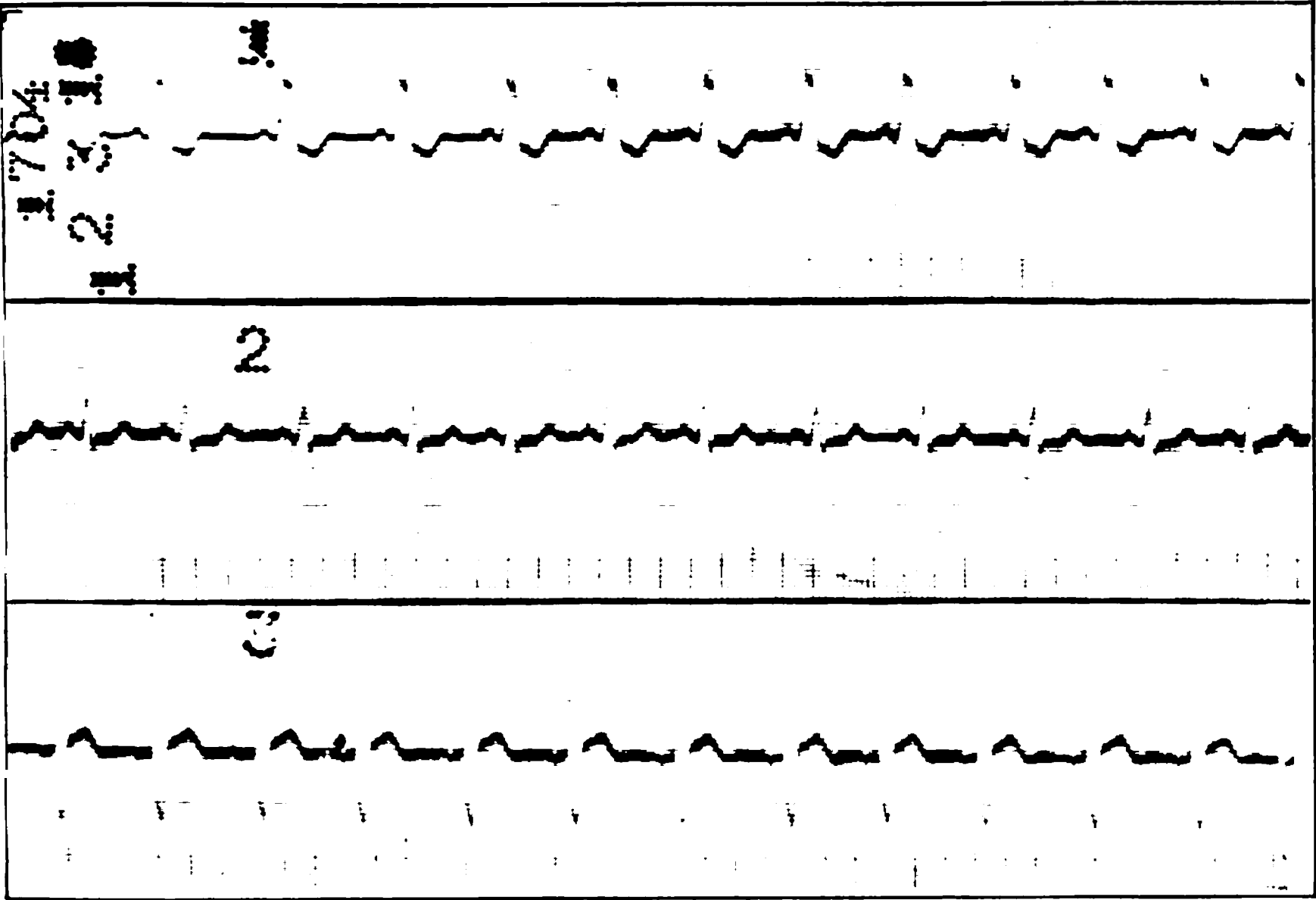
2 L. H. M. L.

value when we have excepted the recognition of the six cardinal irregularities is found in those people who have suffered a definite, localized damage to one of the branches of the bundle of His. This very often is the direct result of rupture, thrombosis or embolism of a vessel of the heart, the occurrence of which is frequently revealed in the history of the person by the story of an attack characterized by severe cardiac pain of long duration with very marked heart failure from which the person gradually recovered. As in the corresponding cerebral event, the lesion may be, and often is, thrombosis, sometimes it is an embolism and occasionally a rupture.

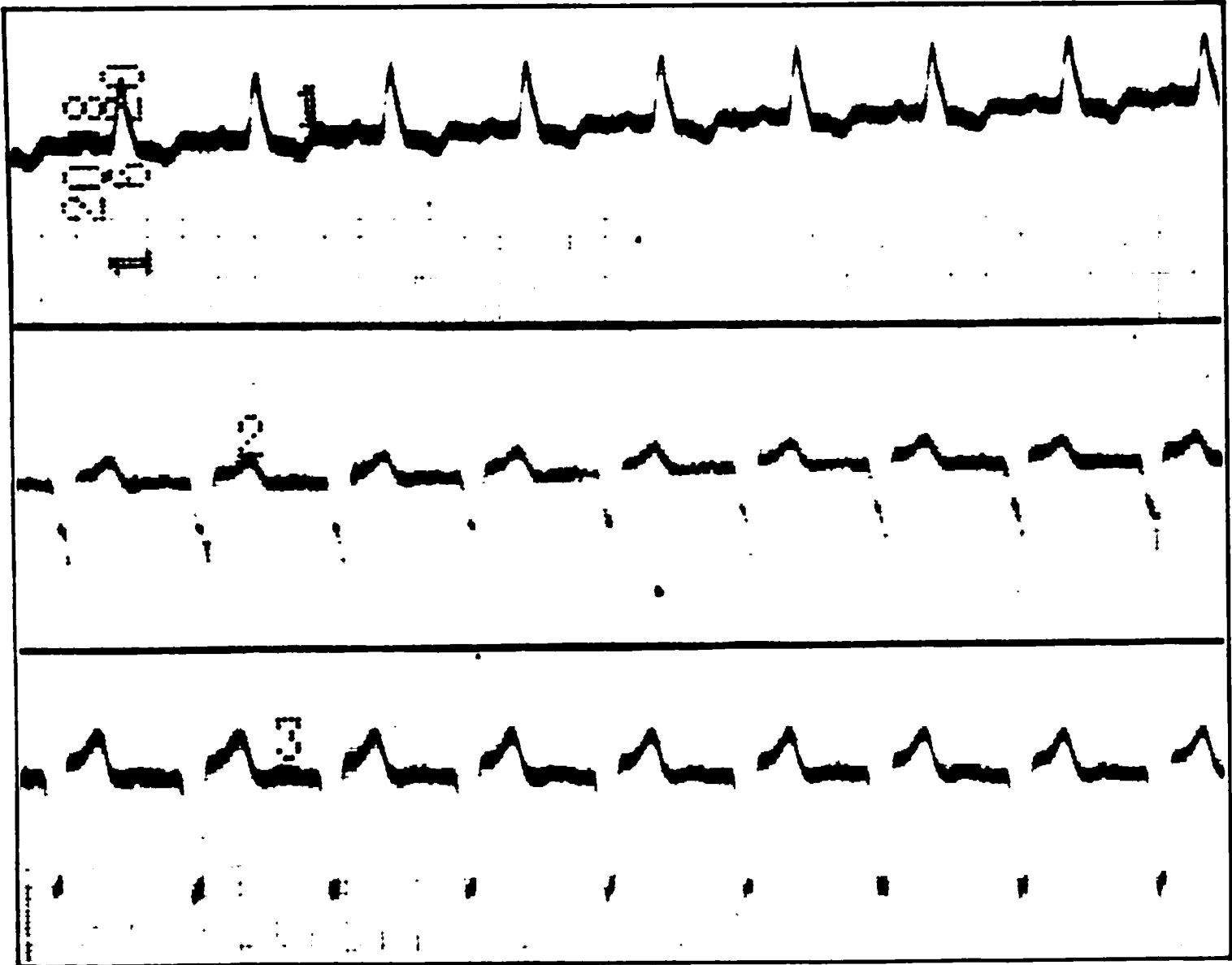
I am showing you about twenty examples of electrocardiographic records which occurred in the last 700 people as examined in my office. This may give you some idea of the relative frequency of this condition, in that group of people whose cardiac condition is of sufficient importance for them to seek a complete technical examination. It also shows that cardiac disease is usually allowed to advance to a high degree of development before people receive the benefit of a close analysis of their heart condition.

In this group of twenty people who were suffering from a disease which involved the terminal branches of the bundle of His all but three were over fifty years of age, and all but four were males. The duration of the disease previous to the time when the patient came to my office was nearly always considerable. In only four patients was it less than a year.

The prominent symptoms of which these people complained were precordial pain, dyspnoea and palpitation. Pain of some sort was present in all but two of these cases and was sharp and severe in eleven. Sometimes it was described as a sense of soreness or a dull pain or a feeling of oppression. The situation of the pain is variable, but nearly always includes the precordium at least in part. In five of the patients the first symptom of disease was pain, while in four the first symptom was shortness of breath. In the remainder of this group the symptoms had rather an insidious onset, and it was difficult for them to say of what they first complained.



3 L. O. D. I.



4 F. T. M. P.

5 L. S. P. L.

6 L. I. O. H.

7 L. I. B. D.

8 L. I. O. S.

Although dyspnoea is usually a prominent symptom, there was one of these people in whom it was not present and another one in whom it was only noticed at night when it came on in attacks.

Palpitation appears in attacks on exertion. It was present in eight of these persons. When present it is usually a distressing and prominent symptom.

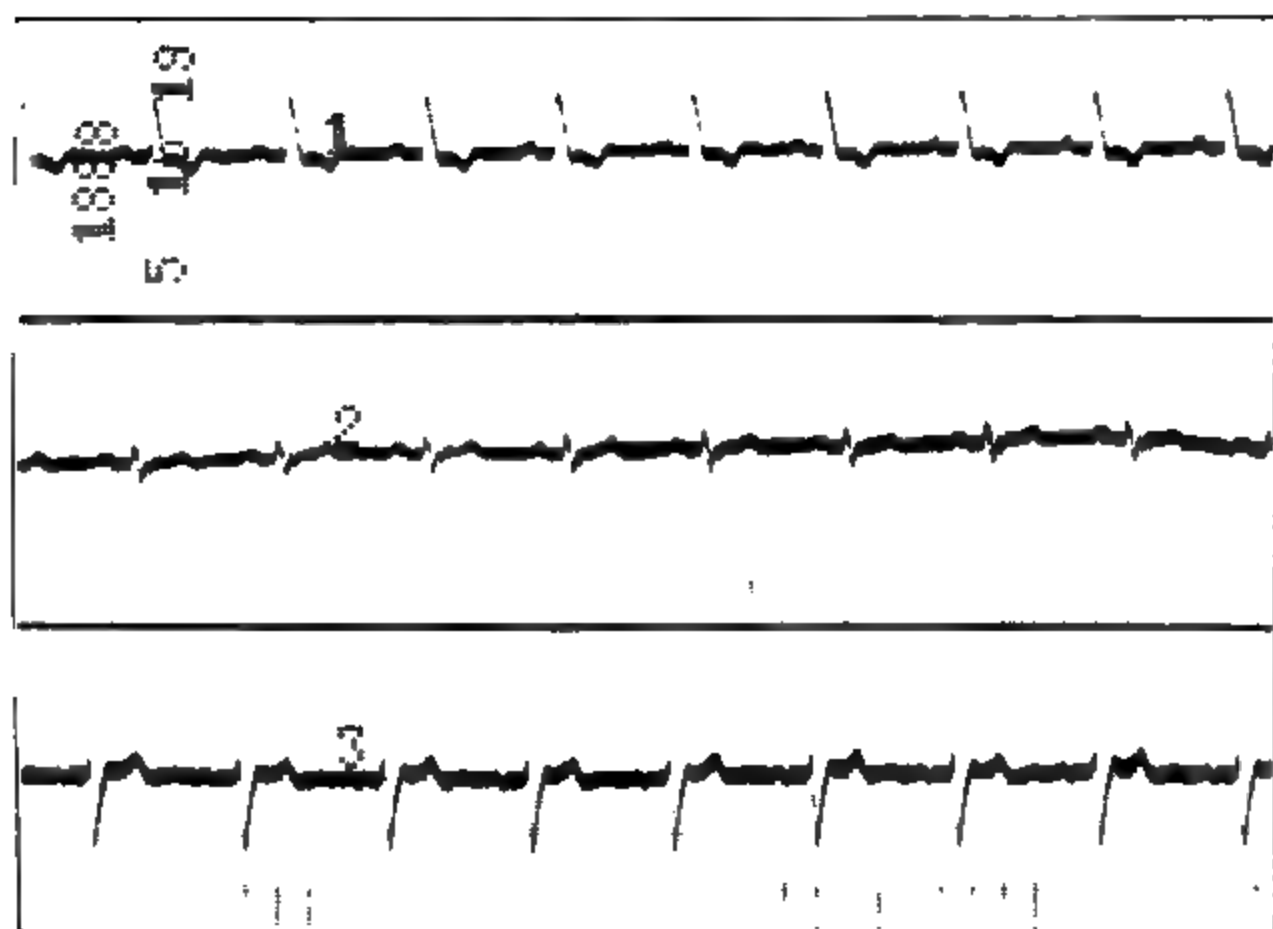
Edema, strangely enough for a condition which is usually considered so serious, did not occur very frequently and when present was not marked, except in one person. Fifteen of these people did not show it.

The weakness of the heart tends to cause a congestion of the lungs which is manifested in cough and this was present in about half of these people. It was not severe, but was very persistent.

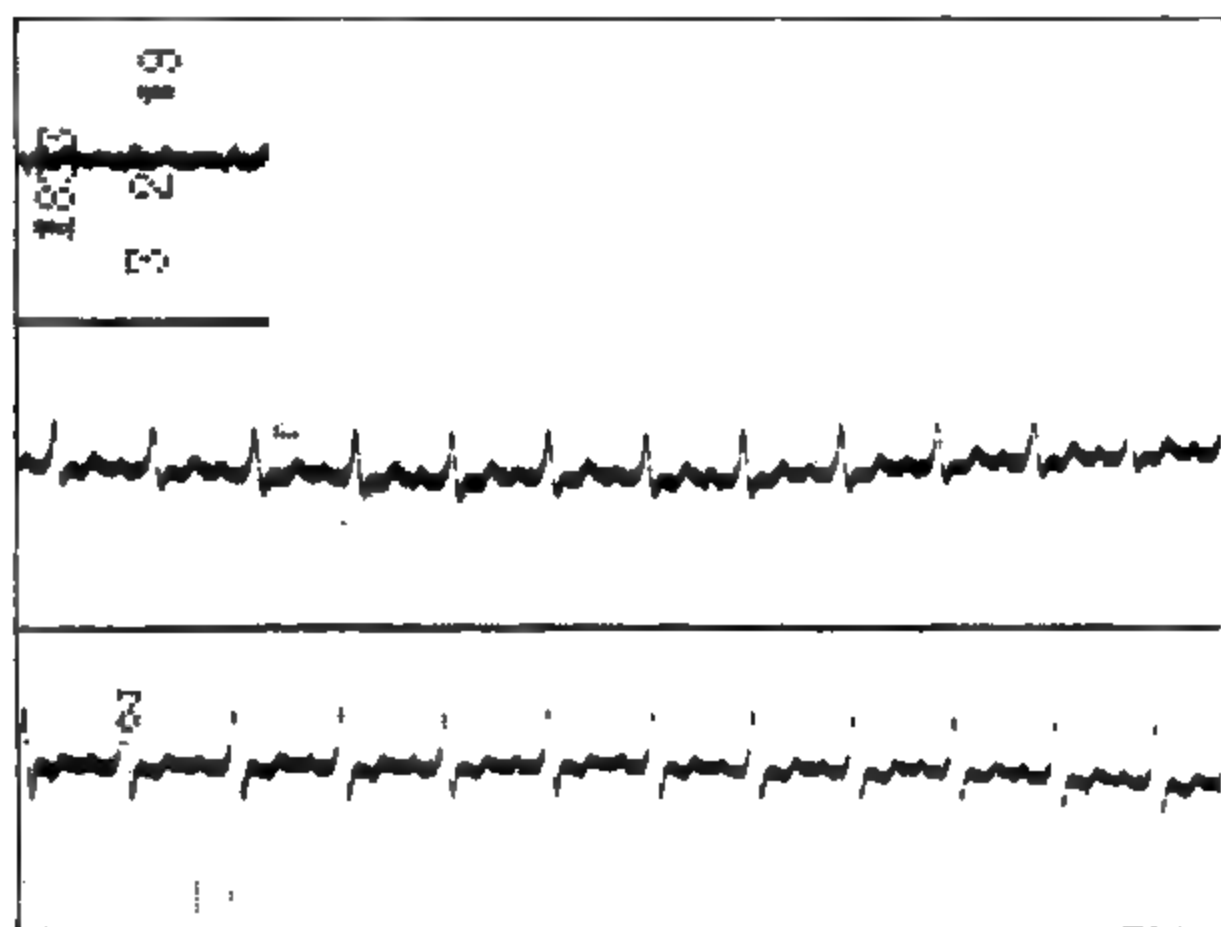
When these people were examined, the most evident thing about them was their age. In going over their records, it is also evident that the majority of them had increased blood pressure, although it is true that some did not show this. Blood pressures in this series were observed as high as 220 mm. for the systolic and twelve of these people gave figures for the systolic which might be considered above normal.

The heart rate was usually not rapid when they came for examination, being over 90 in only six patients, and in only one person was it very rapid, being 120 in that case.

The electrocardiographic record shows the changes which are considered as typical of an obstruction in one of the branches of the bundle of His, in all of these people. The ventricular waves have the large notched Q, R, S group with increased width and the large T wave in the opposite direction, which is typical. All but three of them have the Q, R, S deflection chiefly upward in lead I and downward in lead 3, so that the lesion may be said to be in the right branch of the bundle. The other three records probably have a lesion in the left branch of the bundle. One of the records shows the person had auricular fibrillation, but in all the others the normal rhythm is in force. Three cases showed premature ventricular beats and one showed a prolonged conduction from between the auricles and ventricles.



9 L. P. P. P.



10 L. P. B. B.

The x-ray pictures which were taken of these people by the teleoroentgengraphic method show that four of these people did not have an enlarged heart. Five of them had extremely large hearts and in the remainder there was a moderate enlargement.

It is a very interesting finding that eleven of these patients were considered to have normal valves and in four of them both the aortic and mitral valves were diseased, while in the remainder only one valve was affected.

Eight people showed systolic murmurs at the apex which were not considered to indicate valvular disease.

In our attempts to treat these people, we have been able to observe the response to digitalis in sixteen of the twenty persons and have found that in seven of them it had an extremely beneficial effect. Four were only moderately benefited by digitalis and in five the response was poor.

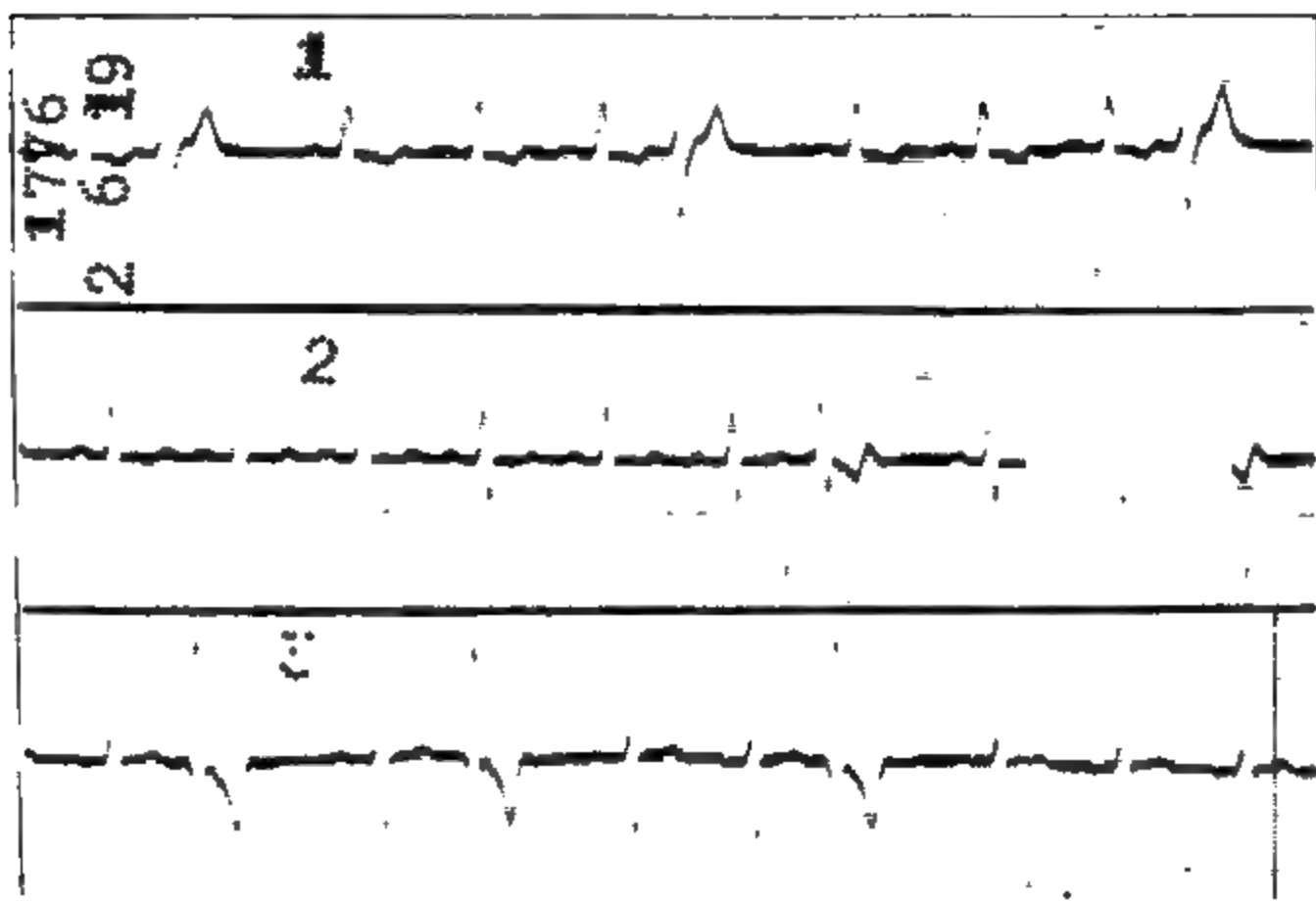
It has been said that all of these people are persons who are well advanced in years and so it is not surprising that our clinical diagnosis, after having reviewed all of the findings, should be arteriosclerosis in eight of these people, cardiac-sclerosis in one other, and angina pectoris in still another. This indicates that these people were suffering chiefly from a condition which goes with age and is not especially brought on by any acute disease.

Five of them were left to go with the diagnosis of myocardial degeneration, while four were believed to have primary valvular disease. In the one remaining person, our diagnosis was cardiac dilation.

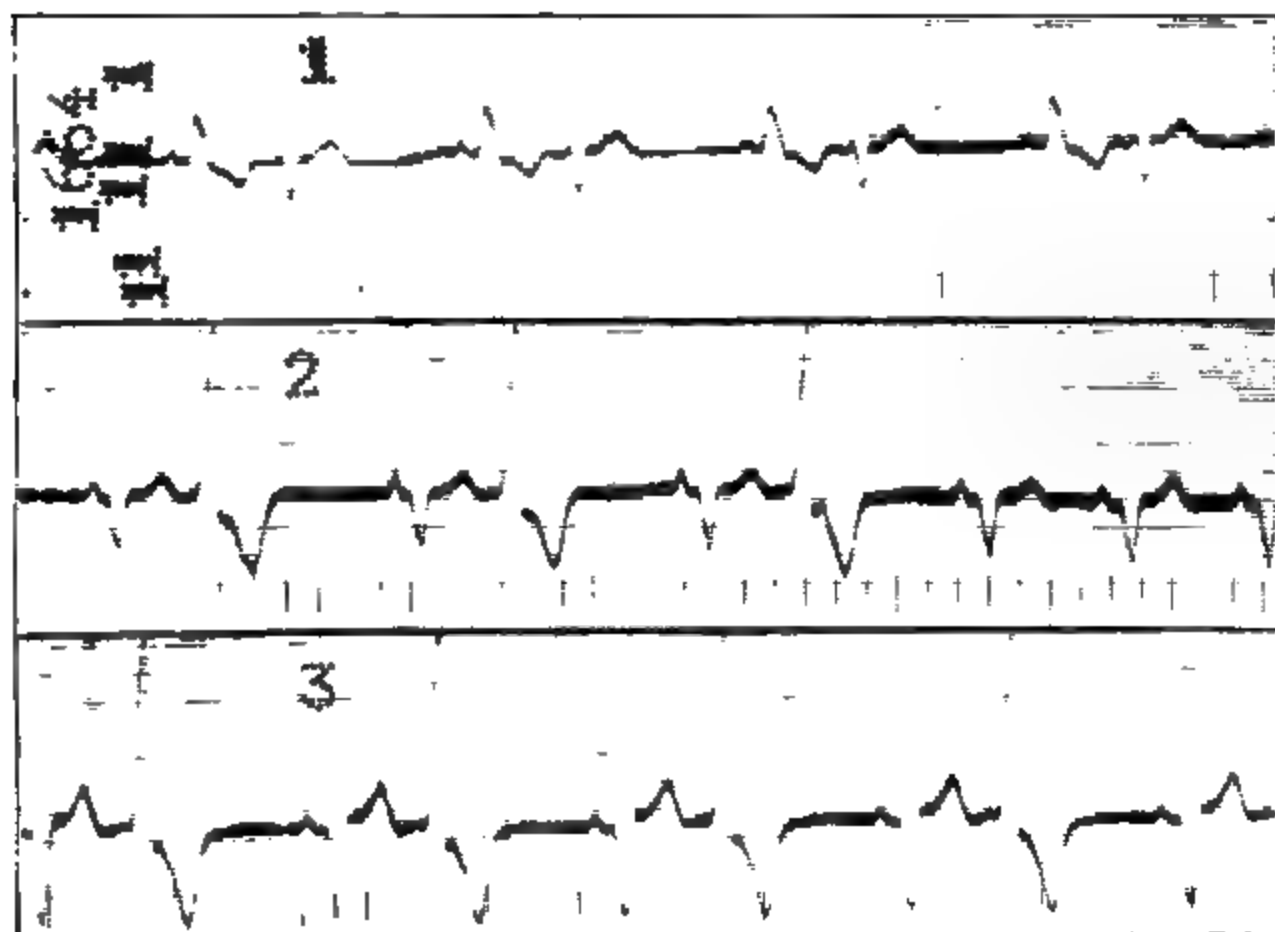
Several of these people, and curiously not those who showed the most striking electrocardiographic pictures, are still under occasional observation and are able to pursue their vocations in a manner that is equal to the average of their age.

All these observations were made in private practice, and bears out the belief expressed by at least one of the greatest heart specialists in the world, that the most fruitful field for the study of cardiology is found in private practice.

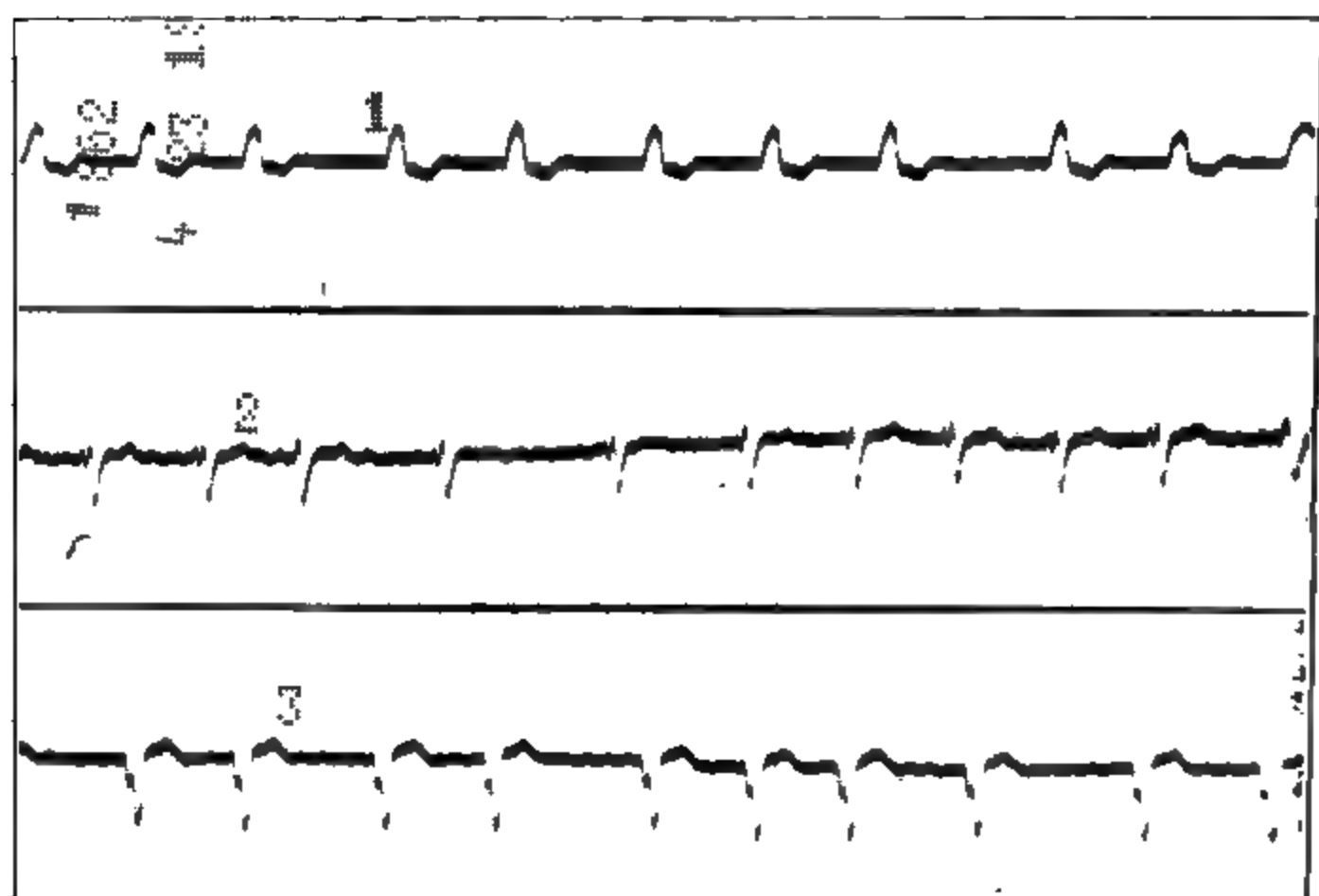
The general condition of the heart must be very good indeed when it can survive and make so good a comparative recovery



11 L. O. O. H.

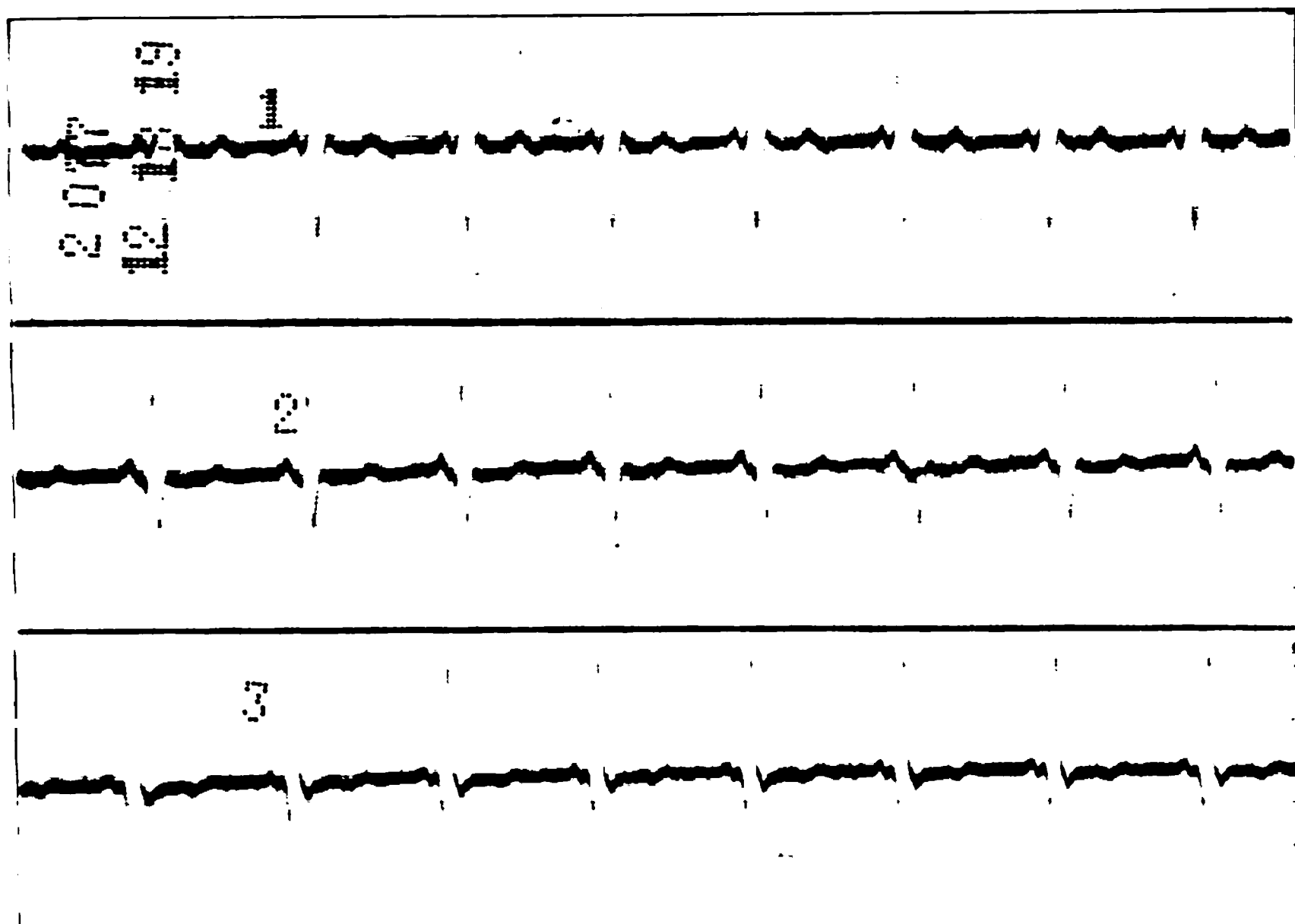


12 L. H. H. I.

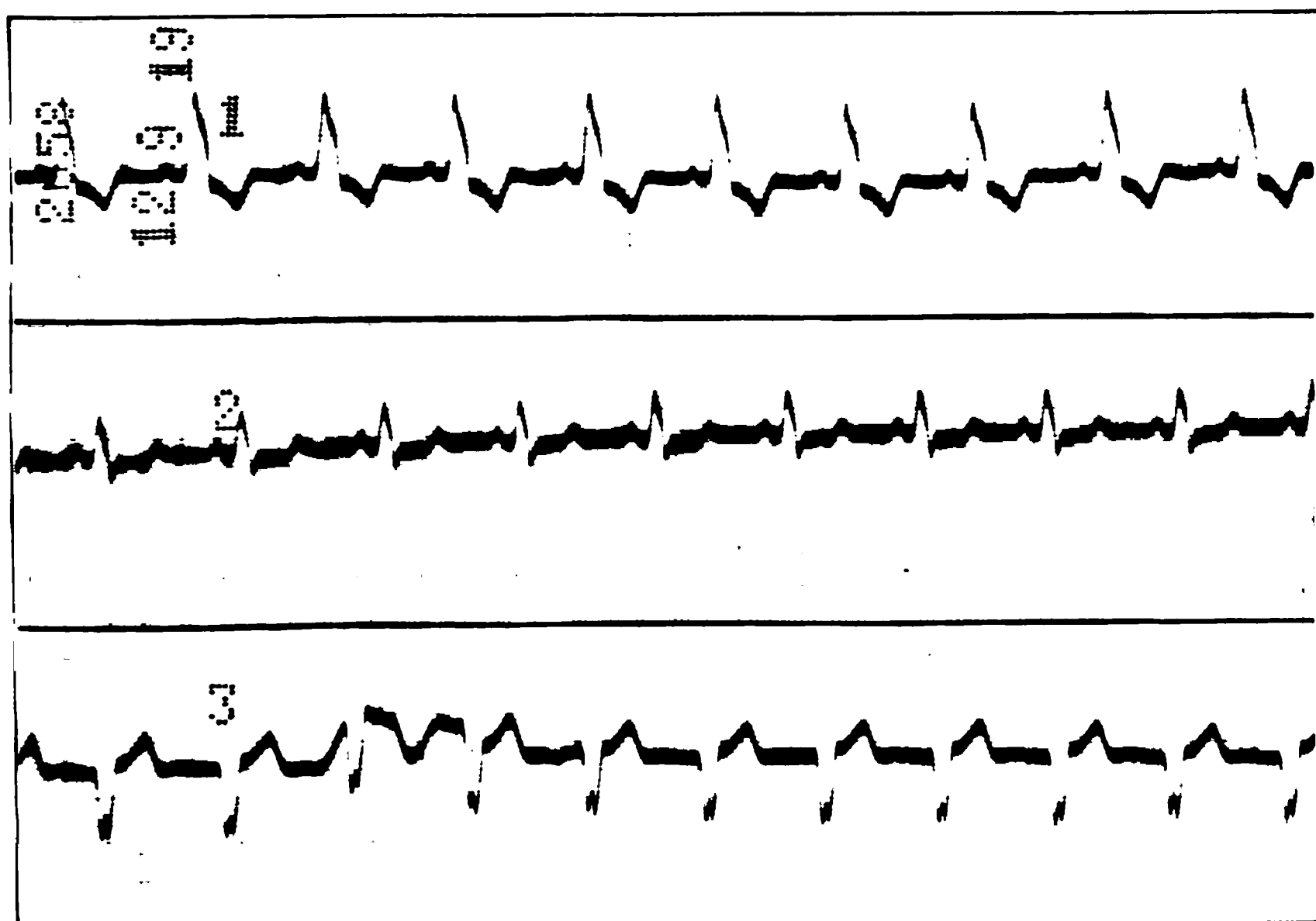


13 L. P. H. I

14 L. P. H. M



15 F. D. O. O.



16 F. D. S. P.

Synopsis of Findings of Twenty Examples of Bundle Branch Lesions.

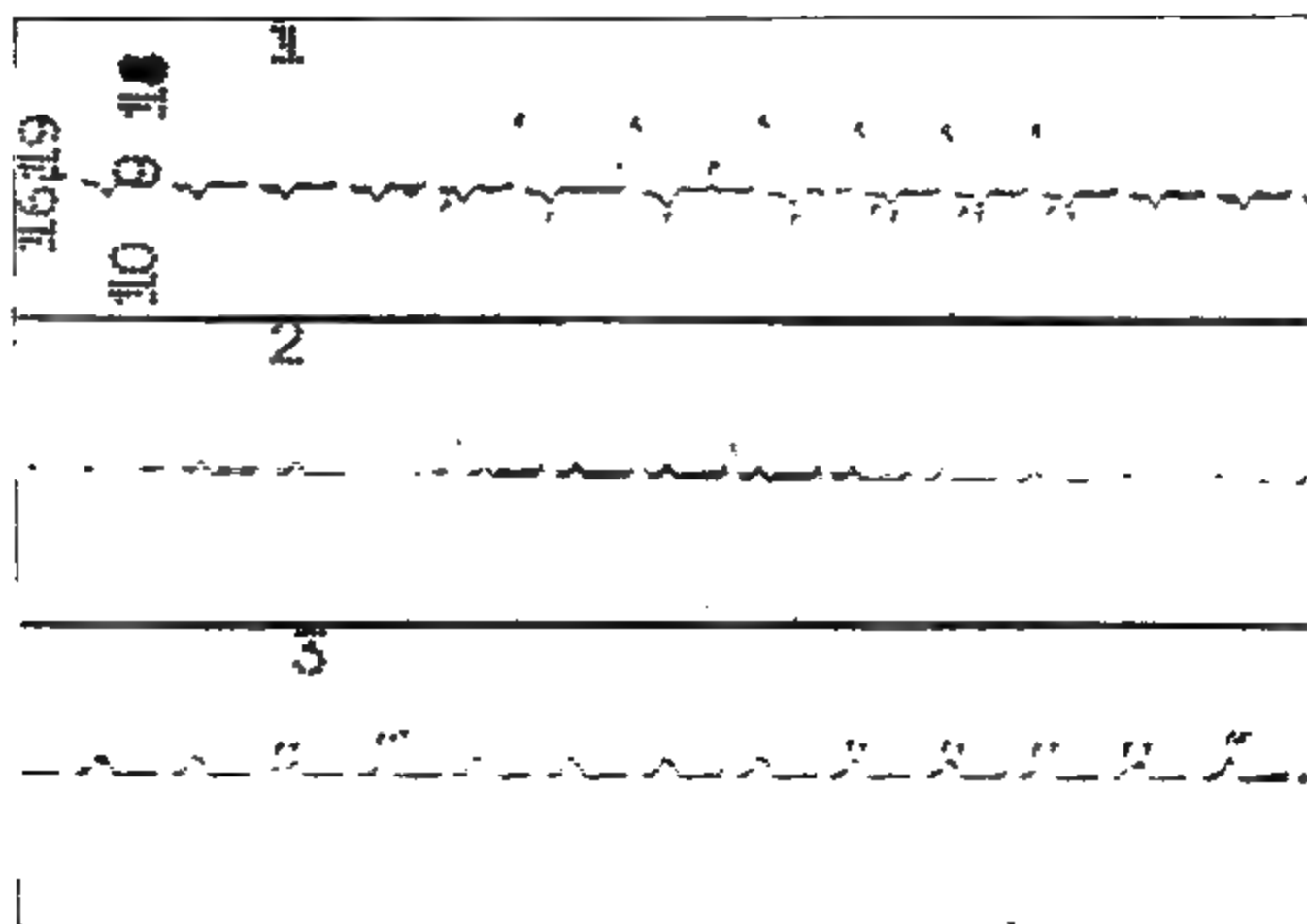
| | Age | Sex | Probable Duration of Disease | Onset | Pain | Dyspnoea | Palpitation | Cough | Edema | Rhythm | Blood Pressure | Valves | Murmurs | Response to Digitalis | Size of Heart | Diagnosis |
|------------|-----|--------|--------------------------------|------------------|---------------|---------------------------|----------------|-------|--------|--------------------------|----------------|------------------------|----------|-----------------------|-----------------------------|-------------------------|
| L.P.P.P.. | 67 | Male | 1 yr. | — | Yes | Moderate | No | No | No | Normal 64 | 150/110 | Moderate sclerosed | No | Good | Large aortic | Arteriosclerosis |
| L.P.B.B.. | 56 | Male | 1 ½ yr. | — | Oppression | On exertion | No | No | No | Normal 96 | 140/90 | Aortic dis. | No | Fair | Normal; dilated aorta | Arteriosclerosis |
| L.O.O.H.. | 52 | Male | 22 yrs. | — | No | On exertion | No | No | No | Normal with ex. syst. 88 | — | Aortic and mitral dis. | No | — | Large aorta | Valvular disease |
| L.H.H.I.. | 76 | Male | Many yrs. | Dyspnoea | No | On exertion | When excited | No | No | Normal with ex. syst. 68 | 210/80 | Aortic and mitral dis. | No | Fair | Moderate enlargement | Arteriosclerosis |
| L.P.H.F.. | 70 | Male | 5 yrs. | — | Stabbing | On exertion | No | Yes | Yes | Auricular Fibril. 75 | 190/100 | Normal | Systolic | Poor | Much enlarged | Myocardial degeneration |
| L.P.H.M. | 57 | Male | 8 mo. | — | Yes | On exertion | Yes | No | No | Normal 77 | 220/148 | Normal | Systolic | — | Very large aorta | Cardiac dilatation |
| F.D.O.O.. | 80 | Male | 5 yrs. Attacks of pain | Attacks of pain | Sharp | On exertion and with pain | No | No | Slight | Normal 68 | low | Normal | No | Good | Large aorta | Angina pectoris |
| F.D.S.P.. | 58 | Male | 12 yrs. Oppression | Oppression | Oppression | None except at night | Yes in attacks | No | No | Normal 88 | 180/90 | Normal | Systolic | Good | Very large aorta | Arteriosclerosis |
| F.D.I.O.. | 68 | Female | 8 yrs. Attack nerv. exhaustion | Attack | Oppression | Moderate dyspnoea | Yes | Yes | No | Normal 70 | 180/ | Normal | Systolic | Good | Considerably enlarged aorta | Arteriosclerosis |
| F.L.I.O... | 47 | Female | 8 mo. Attack of pain | Attack of pain | Sharp | Moderate | No | No | No | Normal 72 | 190/110 | Mitral | No | — | Normal aorta | Arteriosclerosis |
| L.H.L.M. | 53 | Male | 3 yrs. Gradual dyspnoea | Gradual dyspnoea | Sharp | Marked | Yes | Yes | Marked | Heart Block 100 | 160/80 | Aortic and mitral | No | Poor | Very large aortic | Valvular disease |
| L.S.O.D.. | 68 | Male | 5 mo. Attack of pain | Attack of pain | Severe, sharp | Moderate | Yes | Yes | No | Normal 84 | 150/ | Normal | No | Moderate | Mod. large aortic | Myocardial |

Synopsis of Findings of Twenty Examples of Bundle Branch Lesions.—Continued.

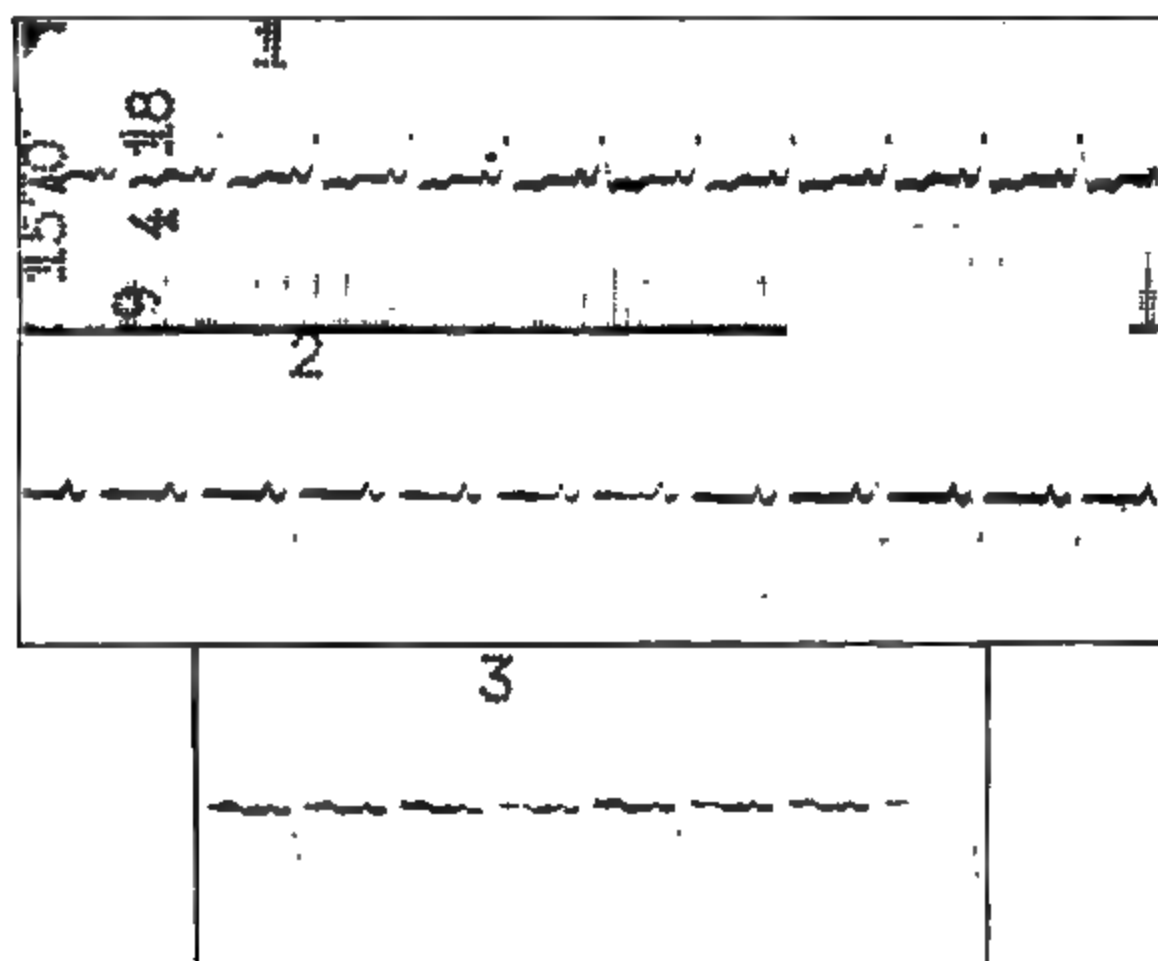
| | Age | Sex | Probable Duration of Disease | Onset | Pain | Dyspnoea | Palpitation | Cough | Edema | Rhythm | Blood Pressure | Valves | Murmurs | Response to Digitalis | Size of Heart | Diagnosis |
|-----------|-----|--------|------------------------------|---------------------|----------------------------|----------------------------------|-------------|--------|----------|--------------------------|----------------|-------------------|----------|-----------------------|--------------------|------------------------------------|
| L.H.B.D.. | 55 | Male | 3 yrs. | Dyspnoea | Soreness | On exertion and attacks at night | Yes | No | At times | Normal 100 | 120/110 | Normal | Systolic | Good | Very large | Myocardial |
| L.H.M.L.. | 26 | Male | Several years | Pain | Dull | No | No | No | No | Normal 72 | — | Mitral | No | Poor | Normal | Valvular disease |
| L.O.D.I.. | 52 | Female | 2 yrs. | Pain | Attacks severe, sharp | On exertion | Yes | Yes | No | Normal 96 | 160/80 | Normal | Systolic | — | Normal broad aorta | Arteriosclerosis |
| F.D.M.P. | 71 | Male | 1 yr. | — | Dull | On exertion | Yes | No | No | Normal 100 | 110/85 | Aortic and mitral | No | Poor | Mod. large | Myocardial |
| L.S.P.L.. | 68 | Male | 40 yrs. | Dyspnoea | Severe attacks on exertion | Bad at times | At times | No | No | Normal 60 | 120/90 | Mitral | No | Good | Large aortic | Rheumatism; cardiac disease |
| L.I.O.H.. | 46 | Male | — | — | Attacks severe | Bad at night and on exertion | No | Slight | No | Normal 75 | 145/110 | Normal | No | Poor | Some hypertrophy | Arteriosclerosis, bronchial asthma |
| L.I.B.D.. | 60 | Female | 5 yrs. | — | Dull | On exertion and smothering | On exertion | Yes | Moderate | Normal 120 | 140/105 | Normal | Systolic | Fair | Mod. large | Myocardial |
| L.I.O.S.. | 64 | Male | 9 mo. | Attacks palpitation | Occas. sharp | Good | Attacks | Yes | No | Normal with ex. syst. 88 | 200/80 | Normal | Systolic | Good | — | Arteriosclerosis |

17 F. D. I. O.

18 F. L. I. O.



19 L. H. L. M.



20 L. S. O. D.

from a definite circulatory accident. It is analogous to the experience that slight attacks of hemiplegia are much better borne and more frequently recovered from among well-cared-for people than among a group ordinarily observed in hospital practice.

The most interesting conclusion to be drawn is that accidental interference with the circulatory system of the heart is probably very frequent and is not confined to those showing very striking clinical manifestations. It is possible that future studies may reveal some means of recognizing such an accident to other parts of the heart muscle. There is certainly much to learn from the study of such groups as these.

109 EAST 61ST STREET.

Discussion:

DR. OPPENHEIMER: It is to be regretted that Dr. Bishop has not had any autopsy material in this series of cases, because at the present time the evidence on which our diagnoses of such electrocardiograms are made, rests largely on experimental work in dogs. The direct application of electrocardiograms resulting from experimental lesions in dogs to electrocardiograms found in man is not certain for several reasons. There are anatomical peculiarities in the dog's heart as compared with the human heart, and the relation of the dog's heart to the chest wall differs from that in man. Moreover, experimentally a single isolated lesion in one of the chief branches of the bundle of His can be produced, but in human pathological material there are almost invariably diffuse, rather widespread lesions involving rather extensive areas of the heart muscle. Recently we have completed the detailed pathological study of two hearts obtained from patients who died in Roosevelt Hospital in the summer of 1914. Dr. Pardee had the opportunity of observing the cases, and of taking the electrocardiograms with the galvanometer in the physiological laboratory, and later we studied the serial sections at the pathological laboratory of the College of Physicians and Surgeons. We found lesions, but not absolutely complete ones, of the chief branches of the bundle of His, but the sides on which the lesions were discovered were the reverse of what we should expect from the results of the experiments on dogs originally performed by Eppinger and Rothberger, and subsequently confirmed by other investigators. In the first of our two cases, the main deflection was inverted in lead I, and upright in leads II and III; microscopic examination showed that the right bundle branch became so attenuated at a distance of 7.5 mm. from the bifurcation that scarcely one or two doubtful muscle fibers could be seen; the left branch presented no lesion. The second case showed, on two examinations, electrocardiograms in which the main deflection was upright in lead I, and inverted in leads II and III. The left bundle branch was imbedded in dense fibrous tissue, and at a distance of 3.5 cm. below its origin, its posterior (dorsal) half was re-

placed by connective tissue continuous with an organized mural thrombus; the right branch was intact. These are only two observations, but they show the importance of the study of human pathological material in addition to animal experimentation in connection with electrocardiography.

DR. BISHOP: I want to thank Dr. Oppenheimer for his suggestion as to the side affected. I had been going chiefly on the empiric way we had been taught. I discussed a good many of these cases with Dr. Pardee, and he seemed to think they were as reported.

I would like to recommend to all of you the study of the electrocardiogram as a most interesting one. I am working with it every day, and every day it reveals something of interest.

A SIMPLER WAY OF PREPARING COLLOIDAL GOLD SOLUTION

MAX LEDERER, M.D.

(From the Laboratory of the Jewish Hospital of Brooklyn)

A perusal of the literature on the preparation of a satisfactory solution of colloidal gold for the detection of reducing substances in the cerebrospinal fluid and the evolution of a diagnostic curve, emphasizes the difficulties with which most workers meet. Most authors utilize some modifications of Lange's original method; either by varying the temperature of the solution during its preparation, or by adding one or more chemicals.

The author has tried most of these described methods and can testify to the inconstancy with which a suitable product has been obtained. For that reason, the following procedure is offered as practically uniform solutions conforming to accepted standards are obtained after almost every attempt.

Solutions prepared in this manner have proven satisfactory in test before use; and clinically, the curves obtained have been checked up by other methods of bedside and laboratory diagnosis. The accompanying charts illustrate some of the results obtained in the wards and laboratory of the Jewish Hospital of Brooklyn.

The glassware used in the preparation of the solution is allowed to soak in freshly prepared aqua regia (U. S. Dispensatory formula) for three days.

Distilled water is made from an ordinary laboratory still. It is used without redistillation; but it is protected from contamination with dust. The glassware just before use is thoroughly

REPORT ON COLLOIDAL GOLD REACTION
Diagnosis, General Paresis

| Dilutions of Cerebrospinal Fluid | | 1-10 | 1-20 | 1-40 | 1-80 | 1-160 | 1-320 | 1-640 | 1-1280 | 1-2560 | 1-5120 | Control | Remarks |
|----------------------------------|-----------------|------|------|------|------|-------|-------|-------|--------|--------|--------|---------|------------------|
| Color Scale | | | | | | | | | | | | | Blood Wasserman |
| 5 | Colorless | | | | | | | | | | | | (++++). |
| 4 | Pale Blue | | | | | | | | | | | | Spinal Wasserman |
| 3 | Blue | | | | | | | | | | | | (++++). |
| 2 | Lilac or Purple | | | | | | | | | | | | |
| 1 | Blue Red | | | | | | | | | | | | |
| 0 | Red | | | | | | | | | | | | |

rinsed with distilled water, and each article is tested with blue litmus paper, the rinsing being continued until no change in the blue color is noted.

REPORT ON COLLOIDAL GOLD REACTION
Diagnosis, Tabes

| Dilutions of Cerebrospinal Fluid | | 1-10 | 1-20 | 1-40 | 1-80 | 1-160 | 1-320 | 1-640 | 1-1280 | 1-2560 | 1-5120 | Control | Remarks |
|----------------------------------|-----------------|------|------|------|------|-------|-------|-------|--------|--------|--------|---------|-------------------|
| Color Scale | | | | | | | | | | | | | Blood Wasserman |
| 5 | Colorless | | | | | | | | | | | | (++++). |
| 4 | Pale Blue | | | | | | | | | | | | Cerebrospinal |
| 3 | Blue | | | | | | | | | | | | fluid (++++)- |
| 2 | Lilac or Purple | | | | | | | | | | | | Globulin-positive |
| 1 | Blue Red | | | | | | | | | | | | |
| 0 | Red | | | | | | | | | | | | |

Into a liter Erlenmeyer flask is poured 500 c.c. of distilled water, accurately measured. Add 5 c.c. of a 1 per cent. solution of gold chloride (Merck and Co.), 3.5 c.c. of 2 per cent. potas-

sium carbonate solution, 0.87 c.c. of 1 per cent. oxalic acid solution and 0.2 c.c. of a 2.5 per cent. solution of formalin. Place over a flame, protecting the base of the flask with a square of

REPORT ON COLLOIDAL GOLD REACTION

Diagnosis, C. S. Lues

asbestos, and heat gently until swirls of water begin to rise to the surface. Adjust the flame so that the temperature of the solution remains at this point, for about 40 to 45 minutes, but do

REPORT ON COLLOIDAL GOLD REACTION

Diagnosis, C. S. Lues

| Dilutions of Centresignial Fluid | | 1-10 | 1-20 | 1-40 | 1-80 | 1-160 | 1-320 | 1-640 | 1-1280 | 1-2560 | 1-5120 | Control | Remarks |
|-------------------------------------|-----------------|------|------|------|------|-------|-------|-------|--------|--------|--------|---------|-----------------|
| Color Scale | | | | | | | | | | | | | Globulin +++ |
| 5 | Colorless | | | | | | | | | | | | C. S. Wasserman |
| 4 | Pale Blue | | | | | | | | | | | | positive +++ |
| 3 | Blue | | | | | | | | | | | | Blood Wasserman |
| 2 | Lilac or Purple | | | | | | | | | | | | 4#. |
| 1 | Blue Red | | | | | | | | | | | | Responded to |
| 0 | Red | | | | | | | | | | | | Asphenamine |

not permit bubbling to occur. At the end of this time the solution should become dark.

When this is noted add slowly drop by drop more formalin solution, meanwhile gently agitating the fluid by a rotatory move-

ment of the flask. Soon there will be seen a brownish red discoloration following in the wake of the formalin drop. The solution becomes darker and darker, changing to a reddish color, and suddenly it takes on the typical old rose hue. The flask is then removed from the flame and allowed to cool.

The amount of formalin used varies in amounts of from about 1.7 to 2.2 c.c. In preparing several batches of solution at the same time, each one may require a different amount. Why this happens we do not know, and no investigation as to the cause of this inconstancy has been attempted by us.

However, in our laboratory, we have met with almost uniform success in every attempt to prepare this fickle solution. It has been used for over a year, and clinically, it has proven satisfactory.

Discussion:

DR. ROHDENBURG: We have been using practically the same technique as that described by Dr. Lederer, and I simply want to reinforce his statement that the bugbear of getting a good solution disappears with that technique. The trouble with colloidal gold solutions seems to be with the formaldehyde. The various niceties of method that have been used, such as the triple distillation of water, etc., have apparently very little influence. We had our first consistent success in making the solution when we received a batch of formaldehyde in one pound bottles instead of in the usual fifty pound carboy. In small containers the formaldehyde does not deteriorate, nor increase its acidity greatly, whereas in a big carboy which is frequently opened and left there is a very marked reduction in the formaldehyde content and an increase in acidity. I think the major part of the technique trouble is due to the variations in the formaldehyde.

DR. STILLMAN: I would like to second Dr. Rohdenburg's remarks about the formaldehyde. We soon discovered that it was the variations in different batches of formaldehyde that caused the trouble. We have been using Lee's method which is also very simple and gives little trouble since we appreciated the variation of the strength of the formaldehyde.

DR. LEDERER: I fully agree that the formalin is the chief factor that we have to deal with. How much of the formalin evaporates on the addition of the formaldehyde as some writers advise I do not know. I think another cause that results in failure is usually the chemical uncleanness of the glassware. I find that some workers are just a little bit careless. They think as long as they do not see any dirt on the glass that they will get good results. I find also that if one avoids the use of soaps that one is likely to get better results. We do not use soaps in the preparation of the glassware. We also use instead of large test tubes small test tubes—the regular Wassermann tubes, 4 x ½ inches, and we can read the end results far better than with the larger tube.

PRECIPITIN FORMATION IN A PATIENT WITH SERUM DISEASE SHOWING IMMEDIATE AND ACCELERATED REACTIONS

GEORGE M. MACKENZIE, M.D.

(From the Medical Clinic of the Presbyterian Hospital, New York City)

Since the pioneer work of von Pirquet and Schick (1) on serum disease, it has been recognized that patients previously treated with heterologous serum may, upon reinjection, exhibit any one of three types of reaction. The type of reaction, or rather, the time when the reaction occurs, depends, they thought, upon the interval between the first and second injections. (1) If the second administration of serum is made twelve to forty days after the first, an immediate reaction occurs. This reaction may be local or general or both, and may be characterized by local œdema at the site of injection, skin eruptions, fever and œdema. The immediate reactions last only one to two days. (2) If the interval between the first and second injections is six weeks to six months, an immediate reaction is apt to occur and also what they called an "accelerated" reaction. In the latter, the symptoms are the same as those of the immediate reaction, but the incubation period is five to seven days; the usual incubation period after a first injection is approximately eight to twelve days. The accelerated reaction like the immediate reaction may last only a day or two. (3) If the second injection is more than six months after the first, only the accelerated reaction is to be expected. The time intervals necessary for these types of serum reaction are subject to considerable variations, von Pirquet and Schick believed.

This patient with serum disease showing both immediate and accelerated reactions was a young man of American birth, 22 years old, admitted to the Presbyterian Hospital, March 21, 1920. Since the condition which brought him to the hospital was of no especial interest from the point of view of his serum disease, only a brief outline will be given.

Chief Complaint: Fever, cough, and pain in left chest for four days.

Family History: Nothing to suggest phenomena of hypersensitiveness in any other members of the family.

Past History: Patient had measles in childhood; pneumonia at the age of eight, and influenza in 1918. Seven years ago he had diphtheria and was given antitoxin. Two years ago, while in the Navy, he had cerebrospinal meningitis and was given anti-meningococcus serum intraspinally. The amount of serum given is not known, but about two weeks later he had a severe attack of urticaria and his eyes swelled so that he could scarcely see. These symptoms persisted several days. He had no recollection of any previous attack of urticaria and had never had angioneurotic edema, eczema, hay fever or asthma.

Present Illness: Four days before admission he had a chill followed by a temperature of 104° F. He had cough, blood-streaked sputum and pain in the left side of the chest.

Physical Examination upon Admission: Temperature, 105.8°. Pulse, 118. Respiration, 20. Patient appeared acutely ill and had signs of a small area of consolidation in the left lower lobe.

Blood Count: White blood cells, 22,400. Polymorphonuclears, 92 per cent. Lymphocytes, 8 per cent. Hemoglobin, 90 per cent. (Sahli). Blood culture was sterile, the Wassermann negative.

Urine: Specific gravity 1.012 to 1.022; acid; albumen, 0; glucose, 0; microscopic showed nothing pathological.

The details of his pneumonia will not be given. It ran an uneventful course; the temperature came down by lysis and the signs in the left lower lobe cleared up promptly.

The interesting feature was the result of giving horse serum to this patient who had twice previously been injected with horse serum—seven years ago for diphtheria and two years ago intraspinally for meningitis. On the latter occasion he reacted with the usual form of serum disease following a first injection.

Upon admission, it was found that he gave a strongly positive reaction to the intracutaneous injection of 0.02 c.c. of a 1:10 dilution of horse serum. Since the usual method employed for desensitizing such patients requires several hours, the house staff started to desensitize him before receiving a report of the mouse inoculation for pneumococcus grouping. It turned out to be a Group IV pneumonia, but this was not known until efforts at desensitization had been carried as far as possible with the idea of preparing him for a large dose of anti-pneumococcus type I serum.

The following table shows how the desensitizing doses of serum were given:

| Time | Horse Serum, Cc. | Method of Admin- istration | Reaction |
|--------------|---------------------|-------------------------------|--|
| 10.30 P.M... | 0.025 | Subcutaneously | None |
| 11.00 " .. | 0.05 | " | " |
| 11.30 " .. | 0.1 | " | " |
| 12.00 M .. | 0.2 | " | " |
| 12.30 A.M... | 0.4 | " | Slight difficulty in breathing |
| 1.00 " .. | 0.8 | " | Erythema, site of injection |
| 1.30 " .. | 1.0 | " | None |
| 2.00 " .. | 0.1 | Intravenously | " |
| 2.30 " .. | 0.2 | " | " |
| 3.00 " .. | 0.4 | " | " |
| 3.30 " .. | 1.0 | " | Swelling, lower jaw. |
| 4.00 " .. | 2.0 | " | None |
| 4.30 " .. | 4.0 | " | " |
| 5.00 " .. | 8.0 | " | " |
| 5.45 " .. | 16.0 | " | Erythema on dorsum of fingers, around left eye and on forehead. |

A few minutes after the intravenous injection of 16 c.c. of horse serum at 5.45 A.M., the erythema became generalized and the patient complained of itching of the hands, back and face. Urticarial wheals appeared over the elbows, wrists and knees. There was no respiratory embarrassment, no œdema nor arthralgia. Five hours later, there was still a diffuse erythema. This gradually disappeared during the next twenty-four hours. Two days later, that is, three days after the administration of horse serum, the epitrochlear and axillary lymph nodes enlarged and there was a generalized eruption which at first was morbiliform and then urticarial. A few purpuric spots were also noted. Soft œdema appeared on forehead, eyelids, nose, lips, forearms, feet and penis. This second serum reaction persisted for six days. The patient therefore showed an immediate and an accelerated reaction, the latter having an incubation period of three days.

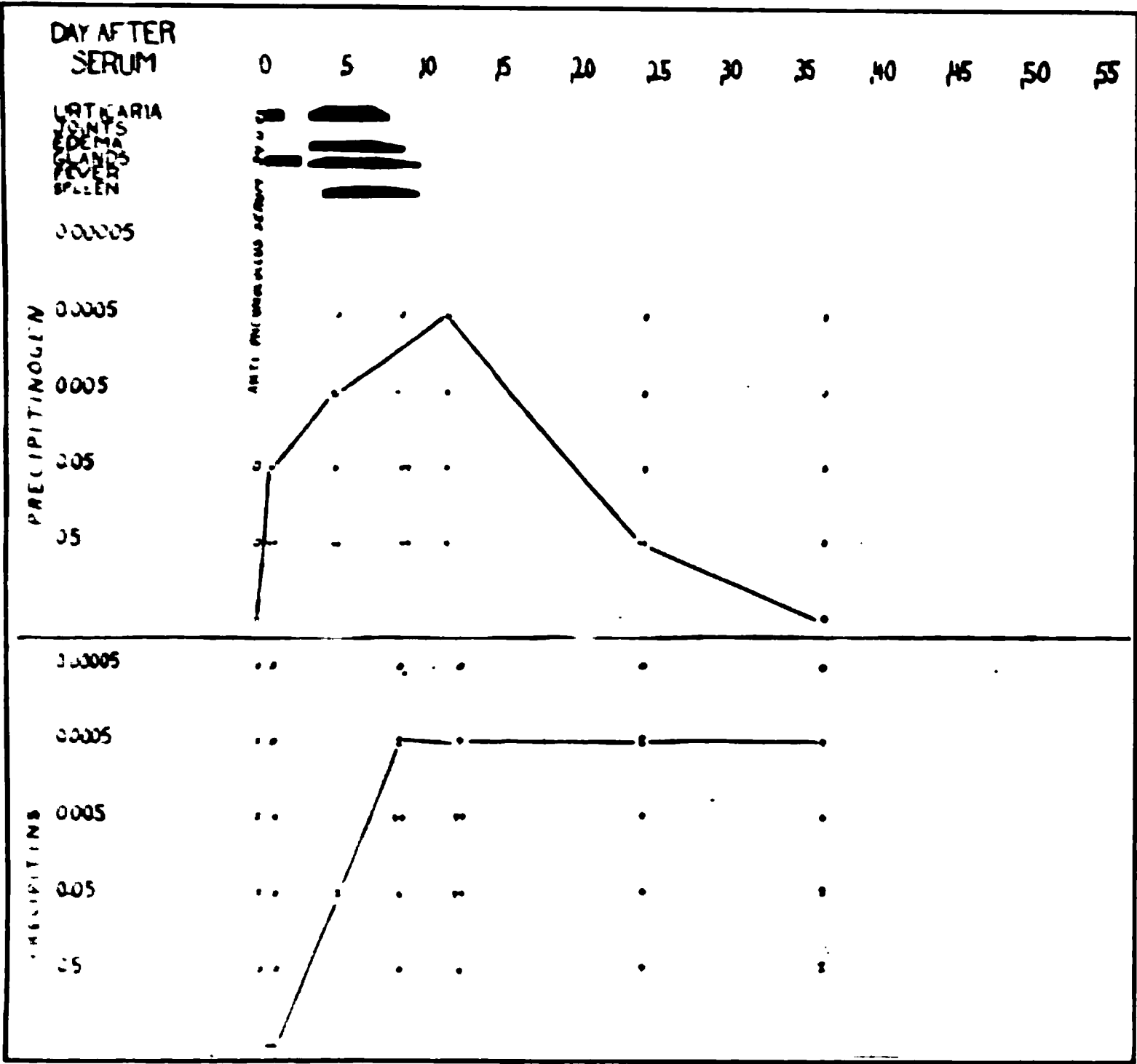
We have been studying the curves of precipitin and circulating antigen in cases of serum disease and it was therefore with a good deal of interest that we followed these curves in this individual who twice previously had been treated with horse serum and who at the time when the 34.0 c.c. of anti-pneumococcus serum were given was demonstrably hypersensitive. Text-figure I represents graphically the development of precipitins and the length of time during which horse serum persisted in the circulation. The relation of these curves to the serum disease is also shown.

There are two points illustrated by this patient to which we wish to call attention.

First, the inadequacy of the Besredka and similar methods of desensitization in man. Besredka's (2) procedure is as follows: One c.c. of a one to seven dilution of the serum is injected intravenously. After 3 to 5 minutes, 3 c.c.; after 2 minutes, 10 c.c.; after 2 minutes, 25 c.c.; after 10 minutes, the patient is considered antianaphylactic and 10 to 30 c.c. of undiluted serum may be given intraspinaly or intravenously. As shown in Chart I we began the desensitization program with a much smaller dose and gave it subcutaneously. We increased the amounts more slowly and gave them at longer intervals than Besredka advises. Nevertheless, when the intravenous dose of 16 c.c. was given, he reacted with such severe symptoms that it would have been dangerous to go ahead with larger doses. It is often stated that a preparatory injection of 1.0 c.c. of serum, subcutaneously, will desensitize a patient so that, after an interval, large doses may be given with impunity. Our experience with this patient shows how inadequate such methods may be with hypersensitive patients.

The second point we wish to emphasize is the accelerated antibody formation parallel with the accelerated symptomatic reaction. After first injections, precipitins usually appear several days after the onset of serum disease, and rise to the crest of their curve synchronous with the termination of the symptoms and the disappearance of the precipitinogen from the circulation. Since the usual incubation period is eight to twelve days, precipitins are rarely found in the circulation earlier than the tenth day. In the paper of Hamburger and Moro (3) precipitins are reported as making their first appearance between the sixteenth and the twenty-seventh day; von Pirquet and Schick (4) state that in children treated with diphtheria antitoxin, precipitins appear toward the end of the third week. In the fifteen cases reported by Longcope and Rackaman (5), precipitins did not appear earlier than the ninth day. Another group of fifteen patients with serum disease after first injection, in whom we have studied precipitin and precipitinogen curves, has revealed only one example of demonstrable precipitins before the ninth day.

It has been repeatedly demonstrated that if rabbits are reinjected after the precipitins produced by a first injection have disappeared from the circulation, that precipitins are formed more rapidly than after the first injection. This patient is an example



TEXT-FIGURE 1. Abscissa represents time in days after administration of serum. The ordinates represent the dilutions of antigen used in testing for precipitin and precipitinogen (horse serum). The results of the precipitinogen titrations are plotted in the upper curve, those for precipitin in the lower. It is seen that precipitin was present on the fifth day, and still present in high concentration thirty-seven days after the administration of serum. With the rise of the precipitin to a high concentration (1-2,000) the precipitinogen curve falls and the symptoms cease.

of the same phenomenon in man. As shown in Text-figure 1, precipitins were present on the fifth day, and they rose to the crest of the curve at the time that the symptoms of the serum

disease were subsiding. The whole process seems to be accelerated after a second injection, so that the incubation period for both symptoms and precipitins is shortened. The precipitins, however, stand in the same relation to the onset and termination of the symptoms. This interesting relation between the precipitins in the circulation and the symptoms of the serum reaction, cannot, of course, be interpreted as indicating that precipitins are responsible for the serum disease. The weight of evidence is in favor of the view that serum disease is an antigen-antibody reaction and that it is only the intracellular antibody which is responsible for the phenomena of the reaction. Precipitins, however, appear in the circulation, sometimes in high concentration, sometimes in low. Just what part the circulating precipitin plays in the reaction, it is not possible to say, but it is nevertheless worth recording that in a hypersensitive individual showing immediate and accelerated reactions, there was also an accelerated appearance of precipitin in the circulation.

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5. LONGCOPE, W. T., and RACKAMAN, F. M.: The Relation of Circulating Antibodies to Serum Disease. *Jour. Exper. Med.*, 1918, xxvii, 341.

Discussion:

DR. JOBLING: I should like to ask if there is any relation between the reaction and the concentration of the precipitinogen in the serum.

DR. MACKENZIE: Apparently there is no definite relation between the titer of the precipitinogen in the circulation and the severity of the reaction.

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DR. JAMES W. JOBLING, *President.*

A TUMOR OF THE THYMUS GLAND

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The rather frequent reports in the recent literature are evidence that tumors of the thymus gland are not as rare as was once supposed. It is with the idea of adding to the existing data that the following case is presented.

The clinical course of the disease in this patient is rather atypical. The tumor occurred in a male, Hebrew, forty-five years old, a furrier by occupation, who had been under observation at varying periods for over three years. He complained on his first admission to the hospital of a persistent cough and after a period of observation lasting five days he was discharged without

a decision as to the origin of the cough. He was again admitted to the hospital a year later, again complaining of cough, profuse expectoration, a loss of weight and shortness of breath. Repeated examinations of the sputum were negative for tuberculosis, although the physical signs in the chest pointed to a widespread and active process involving both lungs. His temperature varied from 98.6° to 102.4° F. He was somewhat emaciated and had lost twenty-five pounds in the year. A radiographic examination of the chest showed a sharply demarcated shadow in the region of the left auricle, and percussion of the cardiac outlines showed an area of dullness agreeing with the radiographic findings. His lungs when examined radiographically showed a picture described as a diffuse tuberculosis. The diagnosis on his discharge was pulmonary tuberculosis, and congenital heart lesion.

He was admitted to the hospital for the last time, two years after his second discharge, and two days before his death. Upon admission, his chief complaint was a furuncle of the lower lip about which there was a diffuse and extensive induration. During his short stay his temperature rapidly rose to a terminal one of 108° F.; he became first maniacal and then comatose, and died of pulmonary edema. He had become so emaciated that his thigh could be spanned with one hand, and it was estimated that he had lost an additional fifty pounds. His relatives stated that the cough had persisted, and that it had become increasingly more difficult for him to breathe. The physical signs in the chest were the same as those on his second admission, except that they were more extensive. Radiographic examination of his chest showed an increase in size of the mass over the left auricle, though it was still sharply demarcated and definite in outline. His pulmonary condition showed little or no change as compared with the process two years previous. His urine contained six per cent. sugar, with acetone and diacetic acid.

At the autopsy the chief point of interest was in the chest, the abdominal viscera showing the parenchymatous degeneration so often seen with septic conditions. Upon opening the chest there presented in the position of the thymus what at first glance appeared to be an enormously hypertrophied gland, the usual configuration being accurately preserved. The gland measured 12 x 14 x 8 cm. in its greatest diameters and overlapped the heart, being tightly adherent to the pericardium. Section through the thymus showed it to be a golden yellow color and to be very firm and resistant on section. There were a few areas of softening in the central portions of the growth. Upon opening the pericardium about 45 c.c. of a clear fluid escaped. On the ventral surface of the heart along the median line were a series of nodules varying in size, the largest being 1.25 cm. in diameter, extending from the main tumor mass. The parietal side of the pericardium showed similar smaller masses. The lungs showed a series of symmetrically distributed hemorrhagic firm areas which on section appeared to be infarcts, and most of which were situated directly beneath the pleura. The larger of these areas measured 2 cm. in diameter. There were no other demonstrable metastases.

Microscopical examination of the tumor showed it to consist of larger

and smaller acini of clear cuboidal cells densely packed together and supported by dense noncellular hyaline connective tissue. Intracellular connective tissue fibrils were not demonstrable. These neoplastic cells were also found similarly arranged in the lesions of the pericardium. In the lung the masses previously described consisted of areas of necrosis surrounded by an inflammatory reaction. In the center of these necrotic areas tumor elements could occasionally be demonstrated.

There is, as is well known, considerable confusion regarding the classification of tumors in the thymus. Ewing draws attention to the fact that while most of the French reports concern carcinoma, most of the German communications describe the neoplasms as sarcoma. Because of this confusion, the term thymoma has been proposed. The tumor in the present instance, however, is to be classed most probably as a carcinoma.

EXPERIMENTAL SYPHILIS

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The interest which an experimental infection holds for the pathologist is as an instrument for the investigation of problems of human disease, and in the case of syphilis there are innumerable problems which have been difficult or impossible of approach on account of the lack of a suitable animal infection. If one wishes to employ an experimental infection for the study of problems of human disease, it is not sufficient that the infection be transmitted to laboratory animals, but it is equally essential that it be brought to a state where the analogy between human and experimental conditions is as close as possible and that one possess an intimate knowledge of both the animal and the human infection. The sequence of events in the development of an experimental infection for such a purpose as I have indicated is, therefore, first, transmission, second, modification and adaptation, third, detailed study of the infection produced, and finally application to problems of human infection.

The transmission of syphilis to laboratory animals is not new; infections differing somewhat in type have been produced in apes, monkeys and rabbits. The infection of apes and of monkeys, although more analogous to the human disease than that originally produced in the rabbit, cannot be very widely used in the study of human syphilis. For such work, the experimental animal should be inexpensive and the rabbit appears to offer the best opportunity for carrying out such studies upon a broad scale.

The difficulty which has arisen in the use of the rabbit has been the nature of the infection produced. Rabbits have been successfully inoculated in the eye, the testicle and various skin areas of the body but it was found that very little developed in these animals except a local lesion at the site of inoculation. It was shown in some instances that the organisms migrated from the point of inoculation and they were recovered from the lymph-nodes, spleen, bone marrow, blood and other organs. In isolated instances, lesions were noted at points entirely removed from the site of inoculation. The first case of this kind was reported by Grouven in a series of communications which appeared during 1907 and 1908. This animal was inoculated in both eyes but infection developed in only one; the eye was enucleated and following this, lesions appeared in the skin and mucous membrane and in the opposite eye; there were marked constitutional symptoms and at autopsy spirochetes were demonstrated in the testicles and regional lymphnodes. As a matter of fact, nearly all of the lesions which have since been described existed in this first case of generalized syphilis in the rabbit.

Other instances of generalized lesions have since been reported but the lesions present were few in number and of a minor character. The most common conditions noted were involvement of the eyes with the production of an interstitial keratitis, papular lesions of the skin and metastatic lesions of the testicles.

When it was found that the disease produced in the rabbit by ordinary methods of inoculation tended to remain a local one and did not lead to the production of generalized lesions as in man,

the attempt was made to produce such a condition by intravenous or intracardial injections of massive doses of spirochetes. After a number of failures, these attempts were in a measure successful in that it was shown to be possible to produce a variety of lesions in animals thus inoculated and that such conditions could be produced with much greater frequency than by local inoculation. It should be pointed out, however, that since the dissemination of organisms in these animals existed *ab initio* in virtue of the mode of inoculation employed, there are some valid objections to considering this type of infection as a generalized syphilis comparable to that which occurs in the acquired form of the disease in man.

This was the status of the subject when we began the study of experimental syphilis. Our interest in this subject originated through an effort to use the experimental infection as a means of studying the action of therapeutic agents but it was soon found that existing knowledge of the infection in the rabbit afforded no adequate basis either for the conduct of the experiments or for the interpretation of results. These limitations naturally obtained also in the study of other problems of human syphilis.

In an effort to meet these conditions, we attempted to gain a more intimate knowledge of the manifestation of infection in the rabbit and to produce an infection which was better adapted to the needs of the investigator. For a period of years, our work consisted largely of observation and record upon material which was being used in the course of other work with little or no opportunity to attempt anything more. In this way, we were able to collect and to study a number of animals which had developed generalized lesions of various types following inoculation in the scrotum or testicles.

The problem which had to be solved if one would reach an intelligent understanding of the experimental infection was why an animal should develop lesions at the site of inoculation but none elsewhere, even though the organisms penetrated the lymphatics or gained access to the blood stream and were widely distributed over the body. At first sight this would seem rather difficult to explain and we did not know whether this dissemi-

nation of organisms was constant or only occasional. The point at which our experimental work began, therefore, was the determination of the time and frequency of generalization of the infecting organisms following inoculation in the testicles or scrotum.

A large number of experiments was carried out for the purpose of determining the presence of spirochetes in the regional lymphatics and the circulating blood. To do this, animals were inoculated in the scrotum by the introduction of a bit of infected tissue; at various intervals after inoculation, the inguinal nodes were removed, ground in a mortar and an emulsion prepared and injected into the testicles of normal animals; the presence of spirochetes in these nodes was decided by the development of an infection in the test animal. In another series of experiments, blood was drawn from the hearts of rabbits which had been inoculated in the testicle or scrotum; after defibrinating, 0.5 c.c. of blood was injected into the testicles of test animals.

In this way, it was found that spirochetes could always be recovered from the inguinal lymphnodes within forty-eight hours after a scrotal inoculation and from the circulating blood within one week after a testicular inoculation, thus showing that a widespread dissemination of the infecting organisms always occurred at a period well in advance of the appearance of the primary lesion.

This being true, the question naturally arises as to why such animals develop no generalized lesions except in an occasional instance? To one familiar with the rabbit infection, the first point which is apt to attract attention is the marked character of the reaction at the site of inoculation. Among the animals studied by us, it was frequently noted that in instances where generalized lesions developed, the primary lesions were very small or slight and this observation gave us our first clue to the cause of the anomalous character of the animal infection.

Upon examination of the records of those animals which had developed generalized lesions, it was found that in the great majority of cases, one of several conditions had existed: Either

the lesion at the site of inoculation had been slight or the animal had been subjected to castration or excision of the primary lesion, or some therapeutic agent had been used which had the effect of reducing the lesion present without destroying the infecting organisms. An investigation of the cases of generalized syphilis reported in the literature revealed the fact that most of these had also occurred under a comparable set of conditions. In this instance, either the animal had been inoculated at one instead of several points or the initial lesion had been excised.

It appeared, therefore, that the presence or absence of generalized lesions was bound up with the primary reaction to infection. We then undertook to determine experimentally whether conditions which tended to reduce or suppress this reaction might not have an influence upon the development of lesions elsewhere. The conditions studied were unilateral as contrasted with bilateral inoculation, the effects of castration or excision of primary lesions, the suppression of primary lesions by the use of therapeutic agents, and the complete prevention of a primary reaction.

The animals were held under observation for three to four months, the results of the experiments being determined by the occurrence of such lesions as could be recognized clinically within this period of time.

The results of the experiments shown on the chart may be summarized as follows:

In group I there were 20 animals which were inoculated in both testicles; 6 were held as controls and 14 were castrated at an early stage of the infection. In this case, 1 of 6 controls developed generalized lesions as compared with 13 of the 14 castrated animals.

In group II there were 27 rabbits inoculated in only one testicle; 13 of these were used as controls and 14 were castrated as in group I. This time, 8 of the 13 controls and 13 of the 14 castrated animals showed generalized lesions.

In a third group of animals, resolution of the lesions was induced by the use of a therapeutic agent administered in doses which were incapable of destroying the spirochetes. There were

24 animals in this group; 12 of them were inoculated in both testicles and 12 in only one testicle. Out of 6 controls in the first series, 1 developed generalized lesions as compared with 5 of the 6 treated animals; in the second series 3 of the 6 controls and all (6) of the treated animals showed well-marked generalized lesions.

In a fourth group of experiments, an attempt was made to determine what effect would be produced if instead of permitting the primary lesions to develop as in the preceding cases, one completely suppressed the reaction at the site of inoculation by amputating the testicle and scrotum forty-eight hours after inoculation. There were ten rabbits in this series which were inoculated in the right scrotum by means of an implant. At the end of the first seven weeks after inoculation, eight of them had developed generalized syphilis which is unusually early and the other two developed generalized lesions before the experiment was concluded, thus giving an unbroken and a very marked series of cases of generalized syphilis.

These experiments appeared to supply a basis for an understanding of the reaction to infection in the experimental animal and at the same time provided means of producing a generalized disease in the rabbit which is more analogous to that which occurs in man. Further than this, I shall not attempt to go.

The next point to be considered is what one means by generalized syphilis in the rabbit. In the generalized disease a variety of lesions occurs chiefly in the skin, the mucous membranes, the eyes, the periosteum and the bones. We have thus far seen practically no visceral lesions with the exception of a few granulomatous conditions which occur in the heart. We know very little of syphilis of the central nervous system. As you know, lesions of the central nervous system have been described, but one must be very cautious indeed in speaking of lesions which occur in the nervous system of the rabbit, since lesions analogous to those which might be produced by a syphilitic infection are found in supposedly normal animals. We have shown, however, that spirochetes do invade the cerebrospinal axis of the rabbit.

We have been able to demonstrate them by inoculation of cerebro-spinal fluid, free from blood, in three animals out of thirteen attempts. One of these was a comparatively early infection and the two others showed active generalized lesions.

The character of the lesions which occur in the rabbit is best shown by illustration. For this purpose we have collected a series of photographs showing the lesions present in representative cases of infection and while they do not include all of the lesions which occurred, they will nevertheless afford a fair impression of the various types of lesions and will show something of the condition which existed in the individual animal. On the whole, they represent the more marked cases of generalized infection.

Generalized syphilis in the rabbit is a very variable condition, as it is in the human subject, and hardly any two animals show precisely the same thing. The lesions usually appear in from two to three months after inoculation and the order in which they appear in different tissues is in general: periosteum and bone, skin and mucous membranes, and finally the eye. The lesions of the several systems vary in different animals. Those of the skin tend to conform to one of two general types. Most frequently they are nodular or tubercular syphilides or they might be called gummata. Again, they resemble more closely the earlier lesions that one finds in cases of human syphilis—there are small infiltrations or macules and papules or maculo-papular lesions showing various degrees of desquamation, exfoliation, necrosis, ulceration and so forth. It is an interesting fact also that the type of lesion present in the individual animal tends to conform to the type of the primary lesion in the scrotum.

The first example which I wish to show is that of an animal with a profusion of small infiltrative lesions of the skin which were distributed about the head and ears, over the forearms, the dorsum and sides of the front and hind feet, and the tail. There were lesions also along the naso-labial margins and in the nasal mucosa. The manifestations of active infection in this animal extended over a period of approximately eight months and the case was one of almost pure cutaneous syphilis.

As a contrast to this, I wish to show a second case of cutaneous syphilis in which all of the lesions were of the large granulomatous type. This animal was inoculated in the right testicle and developed large skin lesions in the scrotum and large granulomatous lesions of the forearm, on the lower eyelid, and on the hind feet and legs. There was also a marked lymphadenitis and a few bone lesions, one of which may be seen at the base of the metatarsal. All of these lesions developed within a period of approximately two months.

A third animal, in which the skin lesions were of the same type as those just shown, furnishes an illustration of a much more pronounced and widespread infection. There was a profusion of skin lesions involving the face, the base of the ears, the front feet and legs, the hind feet and legs and the tail; there were lesions of the bones of the forearm, of the external malleoli and of the long bones of the feet; there were also mucous lesions on the shaft of the penis and about the nares and finally there were lesions of the cornea and iris.

Lesions of the bones in experimental syphilis are among the most interesting manifestations of the generalized infection and this card will show what the common ones are. The most frequent are those which occur about the nose; these are usually periosteal in origin, developing from the outer surface of the bone. They may arise from its inner surface, however, or within the substance of the bone. Lesions in this position frequently result in marked bone destruction and produce a typical saddle nose deformity such as that shown in the radiograph. A second common location of bone lesions is the forearm; the one shown was located near the epiphyseal line of the ulna. The effect upon the bone in this instance is indicated in the corresponding radiograph. The location of lesions near the epiphyses is very common. A third type of lesion is that seen at the base of the fifth metatarsal and these frequently lead to marked destruction of the bone. These illustrations are not all from the same animal but are pronounced or characteristic examples intended to give an idea of the nature of the lesions in the several localities.

The next series of photographs is taken from a case that we might call bone syphilis since with one or two exceptions the lesions present were all of this type. The photograph of the head shows a slight deformity over the nose which does not appear striking at first glance, but the skull of the animal shows marked destruction of the nasal bones. Distinct lesions are seen at the carpus of both forearms. Very pronounced lesions occur also over the external malleoli and others extend along the outer side of the hind feet involving the metatarsals and the phalanges. The animal affording all these lesions also showed a marked lymphadenitis.

At this point, I should like to call attention to the fact that many of the lesions which occur in the rabbit are more analogous to those of congenital than of acquired syphilis and this applies particularly to the lesions of bones.

The conditions shown thus far represented manifestations which arose within a comparatively short period of time. We have, however, similar records of animals which have been held under observation for much longer periods of time—one indeed which is still alive, has been under observation for four years and four months and now shows a lesion of the scrotum which has appeared quite recently. A second rabbit was carried for thirty-three months before it was killed. This group of photographs which was taken from this animal shows some of the most pronounced lesions that we have ever observed. As you see from the photograph of the head taken at autopsy, there was a periosteal lesion of the nose and a lesion in the skin and these had been present for considerably more than a year. Originally there were a number of skin lesions on the feet and legs, some of which are indicated by the very large nodules on the outside of the feet. One lesion on the heel was excised in order to get material for transfer but recurred several times. The photograph is of one of the recurrences. A second lesion with a very interesting history is that at the base of the fifth toe. It was one of the original lesions and persisted from the time of its first appearance until the death of the animal, that is, for more than

two years. Another very persistent lesion of this group is shown on the forearm and this was of approximately thirty months' duration.

This animal also had the most marked eye lesions which we have observed. A keratitis appeared about three months after inoculation; there were repeated exacerbations of this condition and a lesion of the cornea was present when the animal was killed. There were also repeated attacks of iritis, and the photograph of the eye was taken at a time when there was a hemorrhagic iritis.

The lymphadenitis in this animal was also unusually marked; the photographs taken a little more than two years after inoculation show enlargement of the popliteal and the submental glands. At this time, the glands were aspirated and spirochetes were recovered.

Summarizing the work on experimental syphilis which has been presented, the points to be noted are these: First, that through a long series of observations, a number of animals with generalized lesions was collected and studied as accurately as possible with a view to gaining a more intimate knowledge of the experimental infection and through this, some clue which might lead to an explanation of the peculiar character of the infection which follows local inoculation of these animals; second, by applying the information thus acquired, we have endeavored to produce types of infection more analogous to the human disease and in this we think we have been fairly successful. How often such infections can be produced cannot as yet be stated, but from the facts which have been presented, it is evident that a generalized disease can be produced in the rabbit with a considerable degree of frequency.

Discussion:

DR. ZINSSER: I have followed this work with a great deal of pleasure, because it is one of the most systematic studies of animal disease that I have seen. Dr. Brown has obtained lesions that have never been studied with the care and systematic methods he has brought to bear on them. Some of the lesions of course have been seen before, as one cannot help finding them in studying animal syphilis. In our studies on immunity we saw keratitis, bone lesions, and knobs on the nose and occasionally on the long bones, but that

was not the primary object of our study, and I have not the slightest idea what percentage of such lesions we obtained. The first reports of generalized syphilis in rabbits of which I know are those of Uhlenhuth and Mulzer, who claimed that they obtained a generalization of the organism in young rabbits. I would like to know whether Dr. Brown has observed that the youth of the rabbits has anything to do with the generalization. Dr. Brown mentioned one point that interested me particularly, and that is his idea that generalization was encouraged by the suppression of the initial lesion. This has a certain amount of direct bearing upon our work. As Dr. Brown knows we did everything we could to elucidate immunological relations by studying our strain A, both in its virulent condition, and in its culture. We tried all kinds of cross-immunization, but our immunity experiments were entirely negative, with the exception of the local immunity in recovered animals which we have published. An interesting observation which has some bearing on Dr. Brown's work is this: We did a great deal of unilateral inoculation of the testicle, and when we inoculated the opposite testis at any stage of the lesion of the first testis, the tissues of the second testis reacted as though no other inoculation had been made. By that I mean that the tissues of the opposite testis reacted just as though there had been no lesion in the rabbit.

There is another point which would seem to be of interest. For some time we were engaged in a controversy with Dr. Nichols and some others who claimed that there was a difference in the selective action of different strains of *Treponema*. Nichols described a certain strain which he obtained from the nervous system, and with that strain he claimed that he produced lesions in the testis of rabbits that differed from those obtained with other strains. We carried five different strains of spirochetes in rabbits at that time and were able to produce all the lesions described by Nichols with our own strains, and the Nichols strain produced practically all of the ordinary lesions observed with our organisms. The difference seemed to lie in the manner of inoculation. It was at that time also that Dr. Noguchi published the observation that strains of spirochetes differed in thickness and size. We studied our five strains very carefully, and found all variations in size and thickness in all of them. This point is important in that the idea of a specificity of strains and its selective action has taken hold of the clinicians and there has been a great deal written about it. Dr. Brown has had an opportunity to study these different strains in generalized lesions, and I wonder whether he has concluded that Dr. Nichols was right, or whether our observations come nearer the truth. I believe that Dr. Brown will be able to settle that question.

There is not very much more that one can say, except that, though rabbits are poor subjects for studying skin reactions of any kind, it may be worth while to try out luetin on some of these animals. The position of the luetin test is very peculiar just now, and everyone seems inclined to let it rest in peace. It is like so many things that are supposed to be settled, and then come to be doubted again. It is a thing that perhaps these chronic lesions in rabbits might give an opportunity to study. Dr. Hopkins and I made all

kinds of luetin from virulent and from culture spirochetes. We could produce very potent antibodies with culture spirochetes in animals, but found that they had no action on virulent spirochetes. To make a long story short, we never found any serological cross reactions that would bring the culture spirochetes, from which the luetin was made, into any kind of serological relation with the virulent spirochete. The thing was so sharp that I have often in moments of depression wondered if the thing others as well as we have cultivated was really the *Treponema pallidum*. I cannot express such a doubt as a serious contention. It is just a thing which comes to one's mind as a bare possibility. The fact is that Dr. Noguchi, as well as we ourselves, and a considerable number of others, have found that one has to make an enormous number of plants in order to obtain a single *pallidum* culture from syphilitic material, and when the organism is once growing in the test tube, we have shown that it has completely lost its virulence, and has no serological relationship to the virulent spirochete of rabbits or man, and that the serum of syphilitic animals and man has practically no action upon the cultivated organism. This gives one a great deal to think about. It is not at all out of question, of course, that the organism in its cultural state rapidly loses its virulence, and that the virulent spirochete that we supposed at the time of doing our work, is in some way insulated against antibodies. But this matter is by no means cleared up.

DR. LAPOWSKI: May I say a few words from the clinical standpoint? Nobody can appreciate the work of Dr. Brown as much as the clinician can. I was very glad to hear his limitations. He spoke the truth, that all about syphilis is not yet known. It would be a great thing if the clinician would say the same thing. The clinician hears that the laboratory man has developed syphilis in an animal. The laboratory man shows that he obtained certain lesions which look like syphilis and which may be syphilis. But he cannot call it experimental syphilis in the rabbit, as we must first know more about non-syphilitic lesions in the rabbit. I would like to call attention to a fact that was shown in 1914 before the war; unfortunately since that time nobody has taken up the subject. In Vienna Arzt¹ examined normal rabbits and found in them mucous membrane lesions which looked like specific lesions. He found lesions on the scrotum which looked like specific lesions. He found spirochetes in the inguinal glands of the rabbit. He inoculated these spirochetes into another rabbit and obtained a lesion in the skin with *Spirocheta pallida* which could not be differentiated in the dark field from the *Treponema*, and that rabbit was never in the laboratory. Is it syphilis in the rabbit or is it something else? The question is not settled. I would like to ask Dr. Brown whether he examined the skin of the rabbits before he inoculated them, and whether he examined them in the same manner, that is, by palpation, as he says he examined the inoculated rabbits. Of course the Wassermann reaction does not mean anything in a rabbit. The next point is that Dr. Brown fortunately said you could not compare this syphilis with acquired syphilis, but with hereditary syphilis. The lesions have no analogy

¹ *Dermat. Ztschr.*, 1920, Feb.

to acquired syphilis in man. They are rather a spirochetic septicemia. Moreover in skin diseases we have so many manifestations which look like syphilis that it is impossible for any man to make a diagnosis of one lesion and say that it is syphilis. He must have corroboration in the clinical history. I would like to ask if Dr. Brown gives us a clinical history of single rabbits. Dr. Brown is the only man who has observed inoculated rabbits for four years. I would like to know the clinical signs of syphilis in that rabbit. I believe he also had a rabbit under observation for two years. I would like to get the clinical history of syphilis in that rabbit and then you might have a picture of experimental syphilis. You cannot get it by combining the pictures from different rabbits and saying all the lesions look like syphilis. There is one more question about Dr. Zinsser's strains and Dr. Nichols's strain. Dr. Nichols's strain was a nervous strain, that is, it was taken from a spinal cord lesion and not a brain lesion. You cannot call it a nervous strain from a spinal cord lesion. A nervous strain acts differently. But you cannot make out from Dr. Brown's paper which strain is which, and in which rabbit each strain was inoculated. In order to pronounce the rabbit lesions syphilitic, you must inoculate the spirochete from the rabbit lesion into a man. It was done twice by Levaditi unsuccessfully. Nothing developed. Accidentally a man was inoculated into the dorsum of the hand during his work in the laboratory. After thirteen or twenty-eight days a papule developed. The Wassermann reaction was negative on the thirteenth day. The papule corresponded with the inoculated papule in the rabbit. Spirochetes were found in that papule, and the Wassermann reaction on the thirty-fourth day was positive, but no secondary manifestations developed. The man was watched for over six months. During this time there was only a positive Wassermann and no secondary manifestations. If you like to call a man with a positive Wassermann and no manifestations syphilitic you can do so, but that is not clinical syphilis. Another man was inoculated in the arm with the same spirochete, and they got no response. In view of these two facts, that a spirochete is present in the rabbit which cannot be distinguished from the *Spirocheta pallida*, and that inoculation was made into a man and clinical symptoms did not appear, we are still entitled to doubt whether inoculation of the rabbit, even though very successful, would be called syphilis. Surely it is not like acquired syphilis. The clinician watches the laboratory man with great expectation, but the laboratory man must adapt his paper to the clinical aspects of syphilis and pay more attention to the clinical development of experimental syphilis, to make his work of more value to the clinician, which in the end is the main object of the experimental laboratory syphilis.

DR. LARKIN: I was glad to hear Dr. Brown make the statement that he did not have anything new to offer. This work has been gone over very systematically by other workers, and his pictures are perfectly well known to some of us laboratory workers. I thought from the vast amount of work that Dr. Brown has done, and done beautifully, that he might have something to tell us when he said "generalized" syphilis in a rabbit, and that he has

left fairly alone. He also has not mentioned anything about the histological details in regard to this work. He has only demonstrated to us that certain strains of spirochetes may cause experimental lesions. There is a great difference of opinion not only among pathologists, but among bacteriologists, on the different strains of *Spirocheta pallida*. Personally I have not been able to identify these different strains, although they are known as Strain "A," and so forth. But the different characteristics of the spirochetes and their relationship to experimental lesions is not known. We know perfectly well that a spirochete when injected into a testicle, removed and macerated, will produce certain lesions in the skin. The true demonstration as regards the specificity of these lesions in relation to human syphilis is not settled, so that we are not yet in a position to draw any definite conclusions from experimental spirochetal infection in animals and the same lesions which occur in human beings. I do not think that anybody has made any definite statements along that line. Those of us who have studied human syphilis for a number of years may not be so convinced when we look at those lesions in experimental syphilis in rabbits and compare them with those in the human being. I was much interested in this paper because it covers such a wide field, and it has been done in a purely scientific manner. The pictures are beautiful, and the method of presentation, and the deductions, which are very few, have been very interesting. But the lesions are very far from what we know of acquired syphilis, and those we observe in the human being are another question entirely. I was very much interested in the bone and skin lesions, but I would like to know more about generalized syphilis in the rabbit, and the changes that occur in the viscera after the generalization of the spirochete in experimental syphilis. Doubtless the field is so wide that Dr. Brown has not been able to present such questions here to-night. We have a better opportunity of seeing syphilis than any other hospital in the city of New York, because of the great system under which Dr. Fordyce works and the methods which he uses, and the conditions which he maintains in pathological examinations which are conducted under his observation. I wish to express my commendation of Dr. Brown's presentation along this line, because those of us who are interested in the diagnosis and care of syphilis know that everything along experimental lines really amounts to something when the man is intent on his work. My old friend here, Dr. Lapowski, is a perfect iconoclast when it comes to the laboratory man. At the same time he has made some very good points from his clinical experience, that the laboratory man must not stand by himself, but must help and be helped by his clinical brother.

DR. ZINSSER: May I say one more word which may avoid misunderstanding? It is possible that perhaps the two preceding speakers did not understand me correctly. I said that I was a little in doubt when I saw that the serological reactions did not show cross-relations between the culture and virulent spirochete, that perhaps we had cultivated from the rabbit the *Treponema pallidum* which was causing the lesion. I never had any doubt that the lesions which we obtained in rabbits were really lesions of syphilis.

Again, one of the speakers brought out the point that no human infection had ever taken place from rabbits. There are a number of cases of human infection on record. I saw one such infection myself in an assistant who was accidentally infected, and had the entire course, with Wassermann test, etc. The primary lesion was on the face. I have not the slightest doubt that these rabbit lesions deserve to be classified as lesions caused by the *Treponema pallidum*, and furthermore I want to make it perfectly clear that we too have found spirochetal organisms in rabbits that had no connection with the lesions. However, the other spirochetes we found in rabbits were easily distinguished from the *pallida*. Dr. Hopkins and I have published one such case.

DR. LAPOWSKI: Dr. Zinsser, if you have such a case it is your duty to publish it. That case would change everything. Such a statement when it comes from you should be published, in order to give other men the benefit of it, because if that is the case the whole discussion drops.

DR. ZINSSER: Well, that is the case.

DR. LAPOWSKI: Do you mean the case of Dr. Buschke¹ of Berlin, of a laboratory man who accidentally inoculated his finger and developed syphilis? Nobody can prove what that laboratory man did with his finger before and after inoculating it.

DR. ZINSSER: Of course I cannot absolutely guarantee that no outside opportunity for infection took place, but this point was carefully considered.

DR. HOPKINS: I would like to add a word of admiration for this work. I think that one who has worked along these lines and who knows how long it takes to get a few lesions realizes better the immense amount of labor it represents. I would also like to ask one question in regard to the regularity with which Dr. Brown has produced generalized syphilis. While we may have failed to detect some of the lesions, I do not believe that at that time, with our methods of inoculation, the same strain was as frequently producing generalized lesions as it has in Dr. Brown's hands. It seems to me that there are two possible explanations of this. One is the method of inoculation that Dr. Brown is using. The other is a possible greater adaptation of the strain for rabbits after long passage. I wonder whether Dr. Brown has tried to produce generalized lesions with a strain which has not first been carried for many years through rabbits, and whether this generalization of the disease is not a thing brought about by long passage through these animals. I recall that at one time Dr. Brown told me that he had been seeing a certain type of lesion with one strain which occurred for a while, but was not met with later on, which suggested the possibility that the strain had shifted a bit in its characteristics. It seems that that would be a possible explanation for the frequency of generalized lesions in the animals he has described.

DR. CORNWALL: I would like to ask Dr. Brown if the same lesions can be produced by inoculating the whole blood of an individual with florid syphilis as by the inoculation of spirochetal cultures. Is he able to state whether there was any difference in the frequency of histological lesions in the cen-

¹ *Deutsch. med. Wchnschr.*, 1913, xxxix, 1783.

tral nervous system or of the occurrence of spirochete in the spinal fluid between the Nichols's strain and strain "A"?

DR. JOBLING: If I understand correctly, the two strains with which Dr. Brown has been working produce more general lesions now than they did when first inoculated. I would like to ask if monkeys react differently to these old strains. Such experiments might throw some light on the questions of virulence and adaptability.

DR. BROWN: There are quite a number of questions which have been raised, and there seemed to be an oversight of a fact which I mentioned at the outset, that is that the sole purpose of inciting a condition such as that described is to utilize that condition in investigating problems of human disease. Some of us would have all of this work done at once; some are interested primarily in the clinical manifestations of the infection and others in the pathology. As a matter of fact one who works in the laboratory knows that the disease under consideration is a chronic one—that it extends over months and that one person or a small group of workers cannot possibly attempt all of these problems at one time.

In regard to the publications that have thus far appeared, I think that those who are inclined to be critical of omissions should realize that the expense of the work is great and that it is necessary to condense the material as much as possible without detriment to the subject.

In reply to the question as to detailed case reports, I should like to point out that syphilis in the animal or human subject is made up of distinct entities—the case does not make the lesions but it is the combination of these various manifestations which go to make up the picture presented in the individual case. We began the publication of this work, following what we thought was an orderly procedure, taking first the individual manifestations of the infection. As I have said, such publication is expensive, and we have had to condense our material as much as possible so that we have not been able in these earlier papers to supply all of the clinical and pathological connections of the various conditions described. As you noticed in the photographs which were passed around, we have attempted to put some of these clinical manifestations together so as to make up a composite picture of the disease and eventually we shall come to a consideration of the subject from this standpoint.

We also might have gone into the histology or the pathological anatomy of the lesions but we could not attempt so much at one time. We may say, however, that we have worked up the histology of various types of lesions and that we have found no very decided difference between the histology of lesions as they occur in the rabbit, and as we find them in human beings, but they are not identical and I do not think that it is to be expected that a rabbit would react to a given stimulus in exactly the same way as a human being. This is as much as can be said and it would be futile for me to attempt to give a detailed answer to the questions which have been asked regarding the pathology of the experimental lesions.

In answer to the question of the proof of the syphilitic nature of the

lesions I may say that we have not attempted to demonstrate the syphilitic nature of the infection on what one might call a clinical basis. All that we have attempted to do is to obtain a full clinical history of the lesions, to demonstrate the presence of spirochetes in the lesions, to study their histology, and from these facts arrive at a conclusion as to the nature of the condition under consideration. We have not deemed it necessary to investigate the presence or absence of spirochetes in the animal at the time of inoculation but unless the animal showed a lesion of some kind, the assumption seems warranted that the animal was at least not a highly infected one. The work of Arzt and Kerl was a very important piece of work. We have not observed conditions such as they describe and nobody knows what this organism was. The lesions produced were chiefly about the genitalia and I imagine from their description that they were quite analogous to gleet as we find it in rabbits in this country. I think one must recognize, therefore, the possibilities of confusion arising from this source in the case of certain types of lesions and look at this question with perfectly open minds. That is my attitude. Dr. Zinsser has expressed his opinion in regard to the matter of the nature of the spirochete concerned in these experimental infections and the situation may be summed up in the statement that the lesions described are produced in the experimental animal by inoculation of that animal with an organism which has presumably been obtained from cases of human syphilis.

In regard to the question of strains, we have used organisms from five different sources at one time or another; one came from the blood of a syphilitic patient with florid secondaries, another from a chancre, a third from a condyloma, Dr. Zinsser's strain came from a mucous patch, and the Nichols's strain from the cerebrospinal fluid. Whether these are distinct strains or not, I am unable to say. There may be differences in the biological properties of these organisms which are sufficient to warrant one in speaking of them as strains. As has been stated, Nichols claimed that the organism which he isolated produced certain distinctive lesions. We have carried the Nichols and the Zinsser strains through many parallel series of transfers. At first we thought that these strains were producing lesions which were different from one another, but as time has passed, the lesions have changed somewhat so that we cannot say that the lesions produced by any particular organism are more constant for that organism than for others or that the character of such lesions will be maintained through subsequent generations of transfers.

In regard to the part played by adaptation in the production of generalized lesions, we believe that both of these organisms have changed but the high incidence of generalized infections cannot be explained entirely upon the basis of adaptation. This may be seen by reference to the incidence of generalized lesions in the control animals on the chart, which gives the normal incidence following various types of inoculation, and the increase obtained by the introduction of other procedures. We have been able to produce some generalized lesions, if I may term them that, with comparatively fresh strains

of *Treponema pallidum*. We have obtained lesions in the first two or three generations but since these strains were not run in large series of animals, it would be impossible to compare the results with those of the older strains. The lesions were not as numerous or pronounced, however.

Dr. Zinsser mentioned also the resistance of young as compared with old rabbits. In attempting to produce generalized syphilis, Uhlenhuth and Mulzer inoculated their animals intravenously or intracardially. Their impression was that young rabbits were less resistant to infection than the old ones. I have serious doubts of this. As far as I can see, they were giving small animals a few weeks old, a volume dose of organisms which was practically equal to that of the dose given to the largest animals; the effect was to overwhelm the young animal. Our own experience leads us to believe that it would be more difficult to obtain generalized lesions in young than in adult rabbits by using local inoculations.

Someone asked about the production of infection by the injection of human blood. It is my impression that the inoculation of blood from cases of active secondaries has given about as constant results as inoculation of material from lesions. It is not as easy, however, to transfer with the whole blood of the rabbit as it is to transfer with the material taken from the testicle, or from a skin or bone lesion.

The question Dr. Jobling raised of the alteration of the virulence of these strains for monkeys is of importance and I think the general experience has been that as organisms are transferred from monkeys to rabbits or *vice versa* they change their virulence for these animals. We are not certain, therefore, that lesions could be produced by organisms which were transferred to rabbits eight or nine years ago, but, from what we know of such conditions, the failure to infect human beings with such material would be no proof against the syphilitic nature of the animal infection.

There is another question concerning the subject of strains which may be referred to very briefly in this connection. This is one of the most important subjects in syphilis at the present time. It is claimed that there are strains of *Treponema pallidum* which will constantly produce syphilis of a certain type but as far as I am able to judge, no evidence has been submitted which shows conclusively whether these organisms differ in their biological properties, simply on account of their own life history, either in the human or animal subject or whether their biological properties are constant and fixed. In attempting to establish a nervous strain as an entity, distinct from a so-called dermatropic strain, Levaditi and Marie took a very unfortunate basis for comparison. They took a strain freshly isolated from a human source and compared the behavior of this organism with that of the old Truffi strain which had been carried in rabbits for a number of years. Their basis for differentiation rested upon the fact that there was a difference in behavior of these two organisms toward human and animal subjects. The fallacy in such work is quite obvious and I think that we will come to realize that there are many such fallacies which have crept into the work on experimental syphilis.

THE RELATION BETWEEN SPERMATOGENESIS AND
LEUCOPOIESIS IN ACUTE INFECTION

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The purpose of this inquiry is to determine whether the injuries to spermatogenesis so frequently observed in acute infections, are correlated with the injury to the leucopoietic function, as manifested by absence of leucocytosis. This possibility was suggested by the well-known sensitiveness of both spermatogenic cells and leucocytes to radio-active substances and Roentgen-rays. Thirty-eight cases of acute infections in men within the period of active spermatogenesis were chosen as material. The series includes eighteen cases of lobar pneumonia, six cases of influenza, three cases of typhoid fever, and one each of lobular and bronchopneumonia, suppurative pericarditis, suppurative meningitis, suppurative lymphadenitis, acute peritonitis, acute appendicitis, and cellulitis of the forearm. The changes recorded were absence or marked decrease in the number of spermatozoa, spermatids, spermatocytes and spermatogonia, together with the presence of abnormal developmental forms and giant cells. None of the cases selected showed autolytic changes which might confuse the picture. The recent study of Mills on "The Pathological Changes in the Testes in Epidemic Pneumonia,"¹ describes the lesions in detail. Cases showing chronic testicular lesions obviously unrelated to an acute general infection were excluded.

The series is too small to justify an extended statistical treatment. Briefly, it was found that the proportion of cases showing injuries to spermatogenesis increased with the duration of the illness—a point which has already been demonstrated by Mills. The following table illustrates this relation:

¹ *Jour. Exper. Med.*, 1919, xxx, 505.

TABLE I
Relation of Duration to Spermatogenesis

| | | Total Number of Cases | Cases With Lesions | Cases Without Lesions |
|--------------------------|-----------|--------------------------|-----------------------|--------------------------|
| One week | Cases | 17 | 3 | 14 |
| | Per cent. | | 18 | 82 |
| Two weeks | Cases | 11 | 4 | 7 |
| | Per cent. | | 36 | 64 |
| Three weeks | Cases | 6 | 3 | 3 |
| | Per cent. | | 50 | 50 |
| Four to seven weeks..... | Cases | 4 | 4 | 0 |
| | Per cent. | | 100 | 0 |
| Total | | 38 | 14 | 24 |

Not only is there a percental increase in the number of cases showing lesions, according to the duration of the illness, but the qualitative alterations increase in severity with the duration of the infection. The four cases of longest duration showed complete loss of spermatogenesis. On the other hand among the cases which have been classified as essentially normal, there were five which showed slight changes (desquamation of spermatocytes, slight decrease in spermatozoa) which may have been the beginning of more severe lesions. These cases all terminated within eight days.

It is more difficult to establish a definite correlation between leucopenia and loss of spermatogenesis. Taking the total number of eleven cases showing a leucocyte count of 10,000 or less, we find that of these, six or 55 per cent. show definite injury; whereas only eight or 30 per cent. of the twenty-seven cases with a leucocyte count above 10,000 show similar lesions of the testis. This would indicate that, disregarding other possible factors, the testicular lesions are somewhat more frequently found in the cases without leucocytosis. The apparent difference, however, is discounted when the duration factor in the two groups is taken into the reckoning. The mean duration of illness in the six cases of the leucopenic group was 14.4 days, as compared with a mean duration of 9.9 days in the twenty-seven cases of the leucocytic group. One would expect therefore a higher incidence merely on the basis of the longer mean duration of the leucopenic group.

It seems hardly worth while to elaborate further a statistical analysis of this small series of cases. It is evident from the data presented that the duration of the illness is a more significant factor in relation to the injury to spermatogenesis than the possible injury to the leucopoietic function. Certainly it is possible to state that acute infection, such as influenza, accompanied by leucopenia, is not more likely to be accompanied by injury to spermatogenesis than are other infections, like lobar pneumonia, in which a leucocytosis usually occurs.

A discussion of vitamines from various standpoints was given by Dr. Lafayette B. Mendel; no formal paper was presented.

VITAMINES AND THE AVITAMINOSES

CASIMIR FUNK; D.SC.

Whereas the chemistry of the vitamines has not materially advanced during the last seven years, the differentiation of the vitamines, proposed by us in 1912, and which included the anti-beriberi, antiscorbutic and antirachitic vitamines, has been greatly substantiated by the researches made both abroad and in this country. This classification of the three types of vitamines is now accepted by all the workers and can be regarded as a definite step towards progress.

It has also been shown in the last few years, that the value of vitamines reaches beyond their importance for animal life, as it was found that vitamine-like substances play an important rôle in the metabolism of lower animals, bacterias, yeasts and higher plants. In all these new data we see a justification of the term "vitamine" applied to them, showing their importance for the life phenomena of living organisms.

If we leave certain aspects of the beriberi problem to be dealt with later, we come to the consideration of scurvy, a disease so well accepted as a deficiency disease, that it does not leave much

to be discussed. Scurvy is recognized as being due to deficiency of antiscorbutic vitamine (Vitamine C). In dealing with scurvy and the value of certain antiscorbutics, we still meet with certain discrepancies. This, in our opinion, is chiefly due to the use of the guinea pig as a test animal. Let us take as an example, the protective value of fresh meat, already established for human scurvy. Tested on guinea pigs, however, the meat proved inactive. This is due to the fact that these animals require a larger quantity of C-vitamine, as compared with other animals. Harden and Zilva have found in this connection that a guinea pig of 350 gm. requires as much of that substance as a monkey of 2 kg. weight. It is altogether questionable whether we are entitled to test the value of animal foods on herbivorous animals, except when we use these foods in form of easily assimilable extracts. The question of the growth-promoting value of certain antiscorbutics has also received attention. A number of known antiscorbutics, such as orange and other fruit juices, have been found by Osborne and Mendel to contain relatively large amounts of anti-beriberi vitamine (vitamine B). Harden and Zilva have shown that from a mixture of B- and C-vitamines, the first one can be absorbed quantitatively by Fuller's earth, leaving the C-vitamine intact. According to the newest results such filtrates do not exhibit any growth-promoting power. The description of clinical scurvy in older pre-vitamine times was a good deal complicated by pathological findings in the bones, which could have been regarded as rachitic. Since the observation of Hess and Unger, who have seen rosary in cases of uncomplicated scurvy, this subject appears to be simplified to a very appreciable degree.

As regards rickets the known researches of Mellanby have substantiated our earlier contention as to the etiology of this condition. These experiments suggested strongly that rickets is due to the absence from the food of the anti-rachitic vitamine (vitamine A). We are unable to deny, however, that this view has met with a good deal of opposition; Noël Paton considers rickets to be due to a number of causes, a view based chiefly on the old domestication theory of Kassowitz. We must, however, empha-

size the fact that human avitaminoses are evidently not as simple in their etiology as the diseases which we produce experimentally in animals, in which we always endeavor (sometimes even unsuccessfully) to limit the unknown to one single factor. In clinical cases this important presumption is only rarely met with and this applies not only to rickets, but also to the other human deficiency diseases. This remark of course does not pertain to instances which are controlled in a scientific and accurate way, like the researches of Hess and Unger on human rickets, which in this case possess the convincing power of experimental research. These investigators have conducted studies of long duration on children kept on a diet, considered free from vitamine A, and who remained free from all signs of clinical rickets. Dr. Hess gave me the opportunity to see these children and I must confess that I was very much surprised to see them in such good condition. The only signs which might be of importance were a defective enamel of the teeth and a marked delay in walking, whereas a careful X-ray examination did not reveal any signs of rickets. On the other hand, Hess and Unger have seen rickets develop in children on a diet composed of whole milk, which is regarded as being particularly rich in A-vitamine. This condition cleared up on administration of cod liver oil. As the result of these studies, Hess and Unger arrived at the conclusion, that although they believe in the antirachitic properties of cod liver oil, they fail to understand how this condition can be etiologically connected with a deficiency of vitamine A. The chief reasons of these discrepancies can be seen in two factors. First of all, Mellanby, Drummond and others have shown that the requirements in vitamine A diminish with the age of the animal. Mellanby particularly emphasized the fact that quicker-growing dogs were more liable to contract rickets on a diet poor in vitamins A. It seems therefore that in the etiology of rickets, the amount of vitamins in relationship to growth impulse plays an important rôle. Now, in the experiments of Hess and Unger hereditary reasons, limiting the growth, might have played a part in their results.

A second factor, which equally deserves our attention, is the question of the content of foodstuffs in vitamine A. Whereas a few years ago the idea prevailed that only fats and oils of animal origin were carriers of this important substance, these views underwent rapid changes. Through the researches of Osborne and Mendel, McCollum and his coworkers, we know now that green leaves of plants, as well as certain seeds, contain this vitamine in relatively large amounts, whereas butter, once regarded as very rich in this substance, was found in a number of instances to carry only a moderate-amount of A-vitamine. Lately it was asserted that skimmed milk, lard and certain vegetable oils contain this vitamine to an appreciable extent. It seems that the conclusions in the paper published by Macallum and myself in 1915 in which we found no difference in growth of rats, whether we used lard or butter, do not differ as much from our present conception of vitamine A, as they did then.

In view of the constantly changing conclusions as to the vitamine content of various foodstuffs, we wish to emphasize the fact, that the vitamine content is by no means a mathematical unit and that the data obtained in various laboratories in this connection can by no means be regarded as standard values, but must perforce undergo very frequent changes. It may be wrong, for example, to try to compare the vitamine value of European milk, from cows fed in post-war conditions, with milk obtainable in this country. In judging the value of a vegetable, we must not only consider the age (according to the findings of Hess), but also the time elapsed between the removal from the soil and the consumption, the climatic condition, the character of the soil and the amount of fertilizer the farmer was able to apply in each particular case. Vitamine A, according to Hopkins, is very unstable to oxidation, so that in variance with the treatment received, we can easily perceive the possibility of a butter poor in vitamine A, and lard, skimmed milk, cottonseed oil containing this vitamine. It must also be borne in mind that foodstuffs found to be poor in a particular vitamine by the method of biological analysis on rats, may prove to be quite sufficient for human beings. There

are even certain indications in the literature that this may be the case with vitamine A. In this light we must view the above mentioned results of Hess and Unger. By regarding the present accepted vitamine values of various foodstuffs in a critical light, we will be able to explain many of the existing apparent discrepancies in our understanding of deficiency diseases.

After these remarks, we turn to the subject which we intend to deal with to-night, namely the question of the nutritive value of animal proteins as compared with vegetable proteins, with special reference to the etiology of pellagra and hunger edema.

War edema, so frequent in Central Europe during the war, has been ascribed to almost every imaginable cause. After elimination of a number of unlikely factors, among which also the vitamine A was frequently mentioned, many investigators have arrived at the conclusion that this condition is due to deficiency of animal proteins. Kohmann, in particular, was able to produce edema in rats fed on carrots and was able to restore them to health by addition of casein. Whether or not we are justified in regarding this cure to be due to the addition of animal protein as such, we will presently see. McCarrison has found that butter and onions contain a substance which he calls anti-edema vitamine and which specifically prevents changes in suprarenals, which changes ultimately lead to occurrences of edema. During the war there was a long controversy between Hindhede and Rubner, and other German food experts, as regards the value of animal and plant proteins for nutrition. In the light of modern views on pellagra the long continued experiments of Hindhede with potatoes should have led to production of pellagra, which was not the case.

Among the views expressed on pellagra, we find the open-minded attitude of Goldberger, who stated that he was able to prevent or produce pellagra by exclusion or inclusion of foods containing animal protein. His conclusion, which we also share, is that this disease may be due to a variety of causes and possibly to a combination of a number of factors. In the English report on vitamines, which appeared in 1919, we met with the less open-

mind view, that pellagra is due to ingestion of plant proteins of low biological value, with the suggestion that tryptophane may be a factor in the etiology of the disease. Chick and Hume have produced in a monkey a condition which they regard as pellagra, and which was improved upon inclusion of casein in the dietary. Whether it is logically permissible to try to produce a disease, due to lack of animal protein, in monkeys, which never have in their dietary a protein of animal origin, after they are weaned, we cannot say at present. It seems to us, that if pellagra was due to a lack of animal proteins as such, the disease should be more prevalent in countries like Russia or Poland, where the average peasant population does not consume animal proteins more than a few times a year. In spite of this fact, we see pellagra nearly limited to areas of corn consumption. The contention that whole corn is deficient in tryptophane is not borne out by experiments on birds. We can not accept the report of the British medical research committee that pellagra is due to the ingestion of biologically inferior protein.

In our researches of 1913-14 on the influence exerted by carbohydrate portion of the diet, we have observed that pigeons fed on diets containing a larger proportion of casein developed beri-beri later than those on less casein. Recently we have repeated these experiments on rats, in conjunction with Dr. Dubin. These studies, briefly stated, have shown that rats, fed on a diet containing a large amount of purified animal protein, grow on this diet on addition of a small amount of vitamine B, whereas those animals fed on diets containing a large proportion of carbohydrates required a large addition of this vitamine. So that in the presence of animal protein (plant proteins were not investigated as yet) there seems to be a sparing action, as regards requirements of animals for vitamine B and possibly also of other vitamins. It is in this light that we can view the experiments of Kohmann and of Chick and Hume on the curative effects of a casein addition. It is therefore conceivable that a diet containing a sufficient amount of vitamins may prove deficient, if the protein-content of this diet is diluted with a large amount of carbo-

hydrates. An observation, which has not been much emphasized by laboratory workers, is the strange behavior of animals on diets containing all the necessary vitamins, but in insufficient amounts. It would seem that the animal by eating more of this food could obtain all the vitamins it needs, but in practice the reverse takes place and the animal eats less. By increasing the gross metabolism, the animal is unable to overcome the existing disproportion of food constituents. This observation alone should suffice to demonstrate the importance of the relationship of the food constituents and vitamins to each other. It is of interest to note here, that potato, in spite of the great dilution of its protein, seems to constitute a perfectly balanced food for human needs.

Now we must ask ourselves which constituent of an animal protein possesses these important properties, which we have referred to. In studying this question we have derived much information out of investigations conducted with a view of determining the nutritive requirements of certain bacterias and yeast. It would take us too long to consider all the available data and we may select a few which seem to us to be of particular interest. Lloyd, in Cambridge, working on the meningococcus, has found that this microorganism seems to require for its growth a certain vitamin (more or less analogous to B-vitamin) and a substance present in blood, which was absorbed so easily by inert material, that even filtration through ordinary filter paper had to be avoided. Williams in studying the requirements for yeast has seen that hydrolyzed casein possessed a stimulative action on yeast cells, but attributed this action to a contamination with vitamin B. Souza and McCollum have observed a similar action of hydrolyzed beef, although the presence of vitamin B was apparently excluded by experiments on rats. Finally Howard J. Mueller, in working with streptococci, has made the observation that certain hydrolyzed proteins were able to stimulate the growth of this microorganism. He endeavored to isolate the substance responsible for the above mentioned effect, which he believed to be a new unknown aminoacid. He believed this substance to be a new aminoacid for the simple reason that casein used as a start-

ing material was carefully purified by reprecipitation before being submitted to hydrolysis. As the active substance is entirely absorbed by charcoal, it seems that the purification of casein by reprecipitation would not be the right way to free this protein from the unknown substance, as upon each successive precipitation, the condition of absorption will not differ materially from the initial precipitation. This new factor, which seems to differ from all the known aminoacids, acted very much like a vitamine, although it is conceivable that it may ultimately prove to be an aminoacid and a constituent of casein. Just how far this substance is associated with plant proteins has not been investigated as yet. We wish to suggest that this new substance, which apparently has already proved its value for the metabolism of certain bacteria and probably yeast may play a rôle in the etiology of pellagra and war edema, and may explain the contradictory evidence as regards the food value of animal and certain plant proteins. Differences in the nutritive value of proteins of animal origin were also found, in spite of the fact that their analysis did not detect any deficiency of the known aminoacids. To explain this observation, Dr. Sure recently suggested that the nutritive value of the proteins is not only dependent on their composition in aminoacids, but also on their configuration in the protein molecule, certain complexes being better utilized than others. In this way, Dr. Sure explained the nutritive inferiority of lactalbumin. The difference in the nutritive value of casein and lactalbumin may lie in the presence of the above new substance, which in the future we may be able to call vitamine D.

Discussion:

DR. PAPPENHEIMER: With whatever viewpoint one engages in the experimental study of rickets, it is necessary to take reckoning of the spontaneous occurrence of this disease in animals maintained under laboratory conditions. By "spontaneous" is meant the development of the disease under conditions that cannot as yet be accurately defined nor controlled. While such inclusive words as "domestication" and "confinement" bring one no nearer to an understanding of the pathogenesis of rickets, the observation that animals under the artificial conditions of the laboratory are prone to the disease is a very old and well established one.

Anyone who is conversant with the literature on the relation of thymectomy to the production of rickets will appreciate the justice of emphasizing this source of confusion. Now that it has become clear from the work of Renton and Robinson in England, of Nordmann in Germany, and especially the painstaking and carefully controlled work of Park and McClure in this country, that extirpation of the thymus has nothing to do with rickets, it is certain that Klose and Matti and numerous others who thought they had established a definite relation between the thymus and abnormal bone formation were misled by the spontaneous occurrence of rickets in dogs.

In rats also, rickets occurs as a spontaneous disease. Since these animals have become the favorite choice for the study of the effects of dietary deficiencies, it may be pertinent to the topic of the evening to refer briefly to some observations made a number of years ago, and already reported.

It was in connection with experiments on the possible effect of thymectomy in white rats that I had an opportunity to become familiar with the spontaneous occurrence of rickets in these animals. The work was begun in 1913, but it was not until the following spring that the disease appeared among the rats. It affected not only the operated animals but controls of the same litter, and a fair proportion of the stock animals. My interest at that time was centered in the possible relation of thymectomy to rickets, so that no control study was made of the possible dietary factors which might have influenced the development of the disease. It was frequently observed, however, that some animals of a litter became rachitic, whereas others kept in the same cages under identical dietary conditions failed to develop the disease.

There was, of course, nothing original in these observations. Morpurgo, who first described rickets in rats in 1900, studied it for many years and most accurately pictured the lesions. Such connoisseurs of rickets as Schmorl, Weichselbaum and Erdheim recognized the resemblance of rat rickets to that of human rickets and, so far as my own experience goes, I believe that the diseases are pathologically identical. It is therefore obvious that the spontaneous occurrence of the disease at times amongst laboratory rats must be kept in mind in experimental work along these lines.

I should also like to refer to one or two other isolated observations that may bear upon the subject of the evening's discussion. Through the kindness of Professor Sherman, I have had the opportunity to examine two of his rats which had been kept for some time on a diet deficient both in calcium and fat-soluble vitamins. These rats were stunted in their growth and showed at autopsy lesions which at first glance suggested rickets. There were frequent swellings of the chondro-costal junctions and at the shafts of the ribs. The bones were very fragile and broke easily. The histological study of the lesions, however, shows that they are not those of true rickets, but resemble rather the so-called pseudo-rachitic osteoporosis, which results from a deficient amount of calcium in the diet. The little swellings, which

were so conspicuous in the gross, proved to be knobs of provisional callus formed about incomplete spontaneous fractures. There was great rarefaction of the cortex of the ribs with enlargement of the marrow spaces, in contrast to the excessive proliferation of osteoid tissue and the reduction of the marrow spaces which obtains in spontaneous rickets in rats.

I have one other observation which bears upon the possible relation of fat-soluble vitamine to rickets. Dr. Hess has turned over to me for study, ribs from a dog which was kept for five and a half months on one of Mellanby's rachitis producing diets. The diet consists of:

| | |
|-----------------------|----------------|
| Bread | ad lib. |
| Krystalak | 250 c.c. |
| Cotton seed oil | 5 c.c. |
| Orange juice | 5 c.c. |
| Sodium chloride | 1.5 gms. daily |

The histological examination of these ribs gives no indication of rachitic change. The line of ossification is perfectly regular and there is no defect in the deposition of calcium in the matrix of the cartilage or in the new formed bone. The osteoid tissue is not increased. While it is realized that one cannot draw inferences from a single experiment, one can at least say that this individual dog existed for a long time on Mellanby's diet without developing rickets.

DR. HESS: This subject certainly is interesting a large number of medical investigators,—pathologists, biochemists, clinicians, and lately the physiologists and pharmacologists. The progress made has been very great, as one of the speakers said, when we consider that Dr. Funk wrote his book in 1914, and the amount of work that has been done since that time, and the number of difficulties that have been cleared up. On the other hand, the progress has not been entirely steady and uninterrupted. There have been points that have been very difficult to unravel for a year or more, and it is well to consider now what were the difficulties, and whether those we are meeting at the present time are not due to the same causes. Take the fact that we consider foods as chemical entities. One worker will report a result with a certain kind of food, and another worker will report quite a different result, and then after a while it will be found that the two foods are not identical. These foodstuffs cannot be considered as chemical entities. Take for example the question of dried milk. The English investigators at the Lister Institute found that dried milk had practically no anti-scorbutic efficiency. Here we found that dried milk did retain the greater part of its anti-scorbutic efficiency. This question is very clear at present. As Dr. Funk said, milk may be different initially in its anti-scorbutic content; it may be rich or poor. Then the method of desiccation makes a very great deal of difference. It will not stand a slow desiccation, but will stand a rapid desiccation. It will stand 230° F. for a half second or a second, which is the

degree of heat to which it is subjected in the course of drying, but will not stand 150° or 160° for fifteen or twenty minutes. We must bear in mind that the milk may be pasteurized previous to the desiccation and condensed and finally desiccated. So there is a very good reason why one investigator will get one result and another investigator another result. It is so at the present time. One finds lard to be practically deficient in its fat-soluble vitamine content, so that it is used by Mendel as a basic diet. On the other hand, there is a recent report by Miss Daniels that if you use 28 per cent. of the lard it has enough fat-soluble vitamine to maintain rats. The same is true of cotton-seed oil. Each food product must be tested individually, and more than that, we must investigate the particular foodstuff. That is to say, lard must not be considered as lard; cotton-seed oil must not be considered as cotton-seed oil. Each different product must be tested for itself.

From the pathological standpoint there are some questions which are of particular interest, and as Dr. Mendel has said, this entire subject is one which needs the cooperation of the pathologist. In the first place, must we consider that if we get a definite pathological picture that it is due to the same etiological factor? In other words, if you get a picture in an animal or a human being of scurvy, must that be due to a lack of anti-scorbutic vitamine? Or perhaps is there something else that can produce the same pathological picture? We are used to thinking that a pathological picture means a definite disease or disorder. I bring up this question because it has been shown that a lack of the fat-soluble vitamine in the diet of guinea pigs leads to changes very much like scurvy. I have seen the tissues of guinea pigs that had had sufficient anti-scorbutic food in their dietary, that looked very much like the scurvy that I was accustomed to see when they were deprived of anti-scorbutic foodstuffs. On the other hand, there is the question whether we are in all instances dealing with a true rickets or scurvy in our experimental animals. That is another question that must be followed by the pathologists.

Dr. Funk raised the question of whether the guinea pig was a suitable experimental animal for the study of scurvy. It is, I think, too delicate a reagent. It develops scurvy so easily, so much more readily than any other animal, that we must be careful when we transfer such results directly to man. There are no doubt nutritional conditions which can be brought about in guinea pigs which would not have the same result in man. This leads to the conclusion which must always be borne in mind, namely, that after all the final test of all this work is the human being. If you get results on guinea pigs, or on rabbits, or on dogs, or on rats, or on monkeys, and they are absolutely refuted by clinical experience, we must consider whether there has not been some mistake in the experiment, not necessarily a mistake made by the investigator, but whether you can use that particular animal to elucidate the clinical condition.

I should like to say a word in regard to pellagra and rickets. In pellagra Dr. Goldberger believes that the main deficiency factor is a lack of adequate protein. For years during the war the Central Empires were

deficient in adequate protein. They had practically no milk. They had very little meat, and practically no eggs. In other words, they were cut off from adequate protein, and nevertheless pellagra did not develop as far as I know in Germany. When I was in Vienna this summer I asked about pellagra. They had had a few cases there. We should imagine that if this was the dominant cause that pellagra should have manifested itself in the course of the war in the Central Empires. As regards rickets, as Dr. Mendel said, Dr. Bloch of Copenhagen ascribed this keratomalacia to a lack of the fat-soluble vitamine. There was a lack of fat-soluble vitamine also in the Central Empires, and there was no keratomalacia there. On the other hand, Dr. Bloch says nothing about rickets in children, but we hear of what can be called an epidemic of rickets in the Central Empires, and no keratomalacia.

When I wrote not long ago about the relation of fat-soluble vitamine to rickets, I said not that the fat-soluble vitamine bore no relation to rickets, but that it was not the dominant factor, that there are other factors which decide whether or not it shall develop, and I am still of that opinion.

DR. SHERMAN: Perhaps I might say one word about experimental diets that have been used in some of the studies of fat-soluble vitamins. In a number of cases it has been assumed that skim milk could be used in sufficient quantities to be the main source of protein and calcium of the diet, and that diets containing such quantities of skim milk would still be nearly devoid of the fat-soluble vitamine. That, I think, is a mistake. Some years ago Dr. McCollum stated that in a given amount of milk about half of the fat-soluble vitamine is in the fat-globules and about half in the watery portion of the milk. Our recent experience tends to confirm that impression, and on the basis of dry matter, that would mean that dried skim milk has somewhere in the neighborhood of half as much fat-soluble vitamine as dried whole milk. Hence the diets in which skim milk were used probably contained considerably more fat-soluble vitamine than they were regarded as containing.

The eye troubles of rats, which I think are undoubtedly characteristic of a diet lacking in fat-soluble vitamine, can be avoided or cured by skim milk practically free from fat, showing that there is a vitamine which in that respect is the same as the fat-soluble "A," and practically independent of the fat.

DR. MACNEAL: I have been very much interested in the problem of pellagra, not so much in the attempt to demonstrate that it is caused by some particular factor as in the attempt to find out, by sifting the evidence obtained by others as well as that of my own observations and those of my colleagues, what the actual cause of the disease may be. Some of the evidence which has come to light within the past year may be reviewed. Perhaps the first thing to be mentioned should be the publication by Goldberger and Wheeler of the detailed report of their work on convicts at the convict camp near Jackson, Miss., in 1915. This detailed report is somewhat different from the preliminary report, which appeared more than four years pre-

viously. From this later report it appears that the pathological condition which was produced in the convicts consisted of emaciation coupled with a dermatitis of a somewhat indefinite type, which affected the scrotum and the contiguous surfaces of the thighs; that this dermatitis, in one of the earliest cases (McD.—J. M.), itched and was relieved by bathing but later recurred. Although the authors, in their first report, designate the lesions as "typical," they avoid this term in the full report. Here they even suggest that they have some doubt about their typical character, by advancing the view that the site at least of the initial dermatitis is bound up with a specific quality of the diet and by stating that their experimental diet was probably not entirely typical of the average pellagra-producing diet.

The second point of importance is the widely recognized observation, which has been referred to by Dr. Hess, namely, that during the period of the war, when there was a remarkable deficiency in the animal protein in the dietary throughout the central part of Europe, pellagra was quite unknown. It is a disease for which some of us searched in France during 1917 and 1918 without any success whatever. If pellagra is a disease essentially due to deficiency in protein in the diet, it is rather remarkable that it should have been so conspicuously absent in those countries.

A third point of importance is the fact that pellagra did occur during the war, particularly in a large British camp for Turkish prisoners of war in Egypt. Here there were many hundreds of cases among the Turkish prisoners. Many had contracted the disease before capture and a lesser number after capture. The disease actually spread in the camp, however. It became so serious as to be made the subject of investigation by a special Committee of Enquiry. This Committee reported in December, 1918. They found a very extensive outbreak of pellagra among the Turkish prisoners, which they ascribed to a deficient diet, and they contrasted the Turkish camp with the contiguous prison camp in which German prisoners were held and in which pellagra had not appeared. The German prisoners had been living on the fat of the land before capture, and, since capture, had been receiving a diet above reproach. A most dramatic sequel has since come to light. In December, 1918, an epidemic of pellagra began in the German prison camp and a large number of cases appeared in the following six months. Thus, almost at the moment that the dietary experts had pronounced the diet above reproach and had ascribed the absence of pellagra to the excellence of this diet, the epidemic started. Enright, who has reported this outbreak in the *Lancet*, draws the conclusion that he has disproved the relationship of diet as the sole causative factor of pellagra. I think that this very dramatic demonstration has served to change the whole aspect of the pellagra problem as far as the English investigators are concerned.

Evidence pointing to this same conclusion has been furnished long since by American investigators of pellagra and the pellagra situation in this country will still bear further investigation in the light of these developments of the present year.

DR. HAAS: All those who have spoken to-night have called attention to

the fact that this is not a straightforward, clear-cut proposition; that the facts in some respects are proven and definite, but they are isolated facts. It is really a matter for regret that so much lay publicity should have been given to a subject of such importance, in which such excellent work is being done. Mention has been made of disturbing factors in the investigations due to the character and quality of the foodstuffs themselves. No mention, however, has been made of the individual reaction of the animal. Recently I was able to show that at least in the human infant a very definite reaction with consequent growth may be produced by relatively minute doses of atropin, supposedly due to its action on the sympathetic system. The undergrowth of cretinism and the overgrowth of dyspituitarism are too well known to need mention. Herter some years ago called attention to the infantilism which might be the result of a special type of intestinal flora; and so in discussing this problem we are discussing a many-phased subject, and one which in its application to human pathology must be proceeded with very carefully. Take for instance the tomato. It has been fairly well proven to be a satisfactory anti-scorbutic, yet one of the worst cases of scurvy I have seen lately has been fed tomato daily for many months. And so one might go down the list.

The problems of nutrition are so involved and obscure that the greatest caution is necessary in translating laboratory experience to clinical application.

DR. JOBLING: My experience with pellagra in the South makes it impossible for me to accept the theory that this disease is due solely to a dietary deficiency. Particularly does this apply to a deficiency of what some English writers term "biological protein," as I know of instances in which pellagrins have been consuming a very liberal diet previous to the onset of the disease. I have made repeated inquiries concerning this disease of a number of old Southern surgeons, men who were connected with the Confederate armies, and have yet to hear that any of these men, during this period, observed cases of what we now recognize as pellagra. To those who are familiar with the diet of the Southern soldiers during this period this would seem rather strong evidence against the idea that it is due to a deficiency of protein, as their diet in many instances, and for long periods of time, consisted to a large degree of parched corn. Again, if this is true, why should we have had the outbreak of the disease during the period extending from 1910-1914, after which it declined? Are we to assume that the people of the Southern States acquired a hatred for protein substances at this time, and then returned to their former diet? If it is due to a lack of protein, the disease should be very prevalent in Austria, and apparently such is not the case.

DR. FUNK: Workers in this field know that all dietary deficiencies are not necessarily of a vitamine nature and therefore we hardly need to stress this point further. However, we are of the opinion that other fields of nutrition will benefit by the results of vitamine research. We have in mind particularly the chemistry of the proteins and the study of their nutritive

value; here, vitamine research will apparently provide us with new ideas that have been lacking in the last ten years.

We have followed closely the literature on the cattle diseases in South Africa, mentioned by Dr. Mendel. These investigations passed through the various stages typical of a disease whose etiology is unknown, and was finally attributed to a deficiency of phosphorus. This pertains to "lamziekte," but there are other diseases in the same territory, one called "stijfziekte" (apparently analogous to rickets) and another called "poverty." A simultaneous occurrence of diseases, which may be regarded as deficiency diseases, together with a deficiency of phosphorus in the plants, suggests that there might easily be a lack of some other food constituents in the fodder.

We should not be discouraged by the apparently insurmountable difficulties that have been mentioned to-night. Definite progress has been made and whereas a few years ago it was thought that there was nothing further to be known about vitamins, we are at present aware of the fact that we must settle down to real work if all the intricacies of the problem are to be untangled. We must have more constructive and less destructive work.

BESREDKA'S METHOD OF ORAL IMMUNIZATION OF RABBITS WITH OX-BILE AND PARATYPHOID VACCINE

ABRAHAM ZINGHER, M.D., AND DAVID SOLETSKY, M.D.

During the past two years Besredka (1-5) reported from the Pasteur Institute an interesting series of experiments on a method of active immunization of rabbits against the Shiga dysentery, typhoid and para-typhoid B bacillus. This method consists in giving *per os* one dose of a vaccine which has been prepared by heating at 60° C. for one hour a suspension of bacteria grown on agar slants. The principle of this method, according to Besredka, does not depend upon a general immunization of the entire body, but upon the establishment of a local resistance or, as he terms it, impermeability of the intestinal wall. For this purpose the intestinal mucosa has to be partly denuded so as to bring the solitary lymph follicles of the intestinal wall into close contact with the vaccine. With the Shiga dysentery the vaccine alone is sufficient both to denude the mucous membrane and later to render the intestinal wall impermeable to its toxin and endotoxin. In the

case of typhoid and paratyphoid vaccines, however, the intestinal mucosa has to be first prepared by administering to rabbits *per os* on the previous day from 8 to 10 c.c. of ox-bile that has been mixed with some licorice powder. The animals are kept without food until the following morning, when they receive a second similar dose of ox-bile, and two hours later the vaccine through a small catheter.

According to Besredka, this method of vaccination results in establishing an impermeability of the intestinal wall to the living organisms and an insusceptibility of the cells to their endo-toxins, which makes the animals resistant to the infection. Such an infection can be produced in normal rabbits by giving them *per os* bile and a large dose of living bacteria. To obtain uniform results, however, he injected a fatal dose (for the unprepared rabbit) of the living bacteria *intravenously* after preparing the rabbits with bile in the manner described above. After a fatal intravenous injection with the paratyphoid B bacillus, the autopsy shows marked congestion of the intestines, and especially of the Peyer's patches, engorgement of the mesenteric vessels, and a very characteristic muco-purulent inflammation of the gall bladder, the wall of which is thickened and studded on its surface with numerous whitish points. Cultures from the contents of the gall bladder and the small intestines show an abundant and sometimes almost pure growth of the paratyphoid B bacillus. The vaccinated rabbits when tested for immunity are not affected by the intravenous injection of the same dose of the organisms.

To prove that the impermeability of the intestinal wall is the important factor in this form of immunity, Besredka administered *per os* to rabbits that had been prepared with bile a sub-lethal dose of paratyphoid B. bacilli. The agglutinin titer and the serum content in protective substances rose rapidly and reached their height about the twenty-fifth day. On that day the agglutinin content varied from 1:20,000 to 1:80,000 in different animals. At the end of two months the agglutinins were found to be rapidly diminishing. The ingestion at this time of a second dose of living bacteria plus bile did not result in a second increase in

the agglutinins and protective substances. On the contrary, the agglutinins two months later were found to have dropped to from 1:200 to 1:400. Besredka assumed therefore that the first ingestion of the living bacteria produced an impermeability of the intestinal wall, which prevented the living bacteria and their endo-toxin given with the second dose from passing through into the general circulation and causing the formation of immune bodies.

A third factor of interest was shown by the author that the intravenous dose necessary to produce a fatal infection with the paratyphoid B. bacillus in rabbits prepared with bile was only about one tenth of the amount necessary to produce a similar infection in rabbits not so prepared.

To verify these important findings of Besredka we commenced our work by attempting to immunize rabbits with a vaccine prepared from the paratyphoid B. bacillus. The greater practical importance of typhoid and paratyphoid vaccination and the more detailed communication of the author on the use of the paratyphoid vaccine induced us to start our work with this organism.

The culture of the paratyphoid B. bacillus used in our experiments was a strain isolated several years ago in one of the army camps in this country from a case of paratyphoid fever. The vaccine was prepared by growing the bacteria on agar in pint Blake bottles at 37.5° C. for twenty-four hours and heating the suspensions to 60° C. for one hour. Several lots of vaccines were prepared. In some of the experiments a fresh lot of vaccine was used, and in others vaccine that had been kept in the ice box for a maximum of four to six weeks. No difference in results was noted between fresh and preserved vaccine. One dose of vaccine was given except in the case of two rabbits, which received three doses. The multiple doses gave the same result as the single dose. The vaccine was introduced into the stomach through a small catheter.

A standard slant culture was adopted. The test tubes used had an inside diameter of 18 mm., and the slant surface of agar

a length of 50 mm. The culture was grown for twenty-four hours at 37.5° C.

The bile used in most of the experiments was fresh ox-bile that had been passed through a bacteria-proof filter and kept in the ice box until used. Some of the experiments were made with fresh bile that had not been passed through the filter, but no difference was noted in results. The bile was injected into the stomach through a small catheter in order to make certain that the animal received the entire amount (8 to 10 c.c.) with each dose. The routine consisted in giving the first dose of bile during the latter part of the afternoon and keeping the animals without food until the following morning, when they received the second dose of bile. Food was again withheld, and two hours later the vaccine was injected through a catheter. The animals were then allowed to feed as usual.

Group I. Animals Prepared with Bile, Receiving Living Bacteria Intravenously to Determine the Fatal Dose: A series of ten rabbits was injected intravenously with living bacteria in doses varying from one-fiftieth of a slant to one-fifth of a slant. The animals were prepared with bile as described above.

All six animals that received from one fiftieth to one tenth of a slant died at intervals varying from two and a half to twenty-three days. In each case the autopsy showed typical lesions of paratyphoid infection as described above. Pure cultures were obtained from the diseased gall bladder and almost pure cultures from the small intestine. The remaining four rabbits received doses of one-tenth to one-fifth of a slant. These animals died acutely in two to four hours, showing an acute diarrhoea and rapidly increasing muscular weakness. The autopsy was negative with the exception of a general engorgement of the vessels of the mesentery. The dose used in our experiments in testing the vaccinated rabbits for immunity varied from one twenty-fifth to one-eighth of a slant.

Group II. Animals not Prepared with Bile Receiving Living Bacteria Intravenously: There were eight rabbits in this group. The animals were injected intravenously with a dose varying

from one one-hundredth of a slant to a full slant. Five animals receiving doses varying from one one-hundredth to one-third of a slant survived the injection. The animals receiving one-half a slant and one full slant died at intervals varying from one and a half to three days. The autopsies in these rabbits showed a typical paratyphoid infection. It is apparent that the intravenous dose necessary to produce a fatal infection in rabbits prepared with bile is reduced to about one-tenth of the amount that has to be given when the rabbits are not thus prepared. In this respect we were able to obtain results which corresponded closely to those noted by Besredka.

Group III. Animals not Prepared with Bile Receiving Killed Vaccine Intravenously: We thought it advisable to test the toxicity of a killed vaccine by injecting it intravenously in rabbits that were not prepared with bile. The animals died quite promptly in from two to twenty hours. One-half slant produced an acute diarrhoea, marked muscular weakness and death in two to four hours. One-third slant killed the animals in six to twenty hours.

The intravenous injection of the supernatant fluid obtained by centrifuging freshly prepared vaccine in a dose corresponding to the washings of a half agar slant killed animals acutely in three hours. The endo-toxins liberated from the bacteria present in this fluid produced symptoms closely resembling the ones noted in vaccinated rabbits tested for immunity with bile *per os* and a much smaller dose of the living bacteria intravenously.

Group IV. Animals Receiving Killed Vaccine per Os: Eight rabbits received vaccine plus bile. The heated vaccine was given in a dose corresponding to one fourth of the growth on a pint Blake bottle. Agglutinin tests at weekly intervals made during the following five weeks gave negative results. Four of the eight animals were tested for immunity at the end of three weeks by preparing them first with bile and then injecting them intravenously with a fatal dose of the paratyphoid B. bacillus. None of the animals showed any immunity, three of the rabbits dying even more rapidly than the normal controls.

Three rabbits received vaccine alone without bile. Here we expected no immunity, as Besredka had stated that preparation with bile was essential in producing local resistance of the intestinal wall. No agglutinins were found in subsequent bleedings. When tested for immunity from three weeks to two months later the animals succumbed in from two hours to four days.

Group I'. Animals Receiving Living Bacteria per Os: Four rabbits were prepared with bile and received living bacteria in a single dose, varying from one-fourth to a full surface culture from a pint Blake bottle. The suspension of the living bacteria was injected through a small catheter. Agglutination tests in dilutions of 1:50, 1:100, and 1:200 at weekly intervals during the following four weeks gave negative results. Three of these animals were subsequently tested for immunity, two at three weeks and one at six weeks after receiving the living bacteria *per os*. Two of the rabbits died rather promptly and one survived. This animal had been tested with one-fifteenth of a slant and was re-tested two months later with a larger dose—one eighth of a slant. The animal died at the end of five days, the autopsy showing the typical picture of paratyphoid infection.

Three rabbits that had not been prepared with bile also received living bacteria *per os*. In this group we expected to find no immunity. One animal died of an intercurrent infection, the two surviving ones were later tested for immunity with negative results.

Conclusions

1. No immunity was obtained in rabbits prepared with ox-bile and given living or dead paratyphoid B. bacilli *per os*.

2. No agglutinin production was noted in rabbits receiving living or dead bacilli *per os* either with or without bile.

3. The intravenous fatal dose of paratyphoid B. for rabbits prepared with bile was only about one-tenth of the amount required to produce a fatal infection in rabbits which were not so prepared.

4. The killed vaccine of the paratyphoid B. is more toxic than the suspension of living bacteria.

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Discussion:

DR. HUNTOON: I must confess that I am disappointed. I came miles to learn the successful technique, and now Dr. Zingher tells us that it cannot be done. This paper of Besredka's of course awakened everyone on the subject of immunization, because it takes up the whole question of what immunity is. There is some evidence, more or less scattered, that the resistance of an animal to infection really resides in the cell. Some years ago Dr. Elser and myself fed rabbits typhoid bacilli, living, but put in capsules. I remember feeding the rabbits the capsules every morning. Then we tested the rabbits' blood weekly for agglutinins. We found nothing until one rabbit developed apparently a spontaneous diarrhea, promptly followed by the appearance of agglutinins in the blood. We could not isolate typhoid bacilli from the stool. We took the other rabbits and injected them intravenously with killed meningococci because we knew that this caused lesions to appear in the intestinal wall. Very promptly agglutinins for typhoid appeared in the blood. We found that they were common agglutinins for typhoid, colon and para-typhoid. I would like to ask Dr. Zingher if he used para-typhoid B. If so, that would account for the early deaths with the larger doses.

DR. EWING: I think it would have been of interest for Dr. Zingher to have determined whether the administration of bile did actually denude the epithelium. I think this point deserves proof. Did Besredka put the bile through a Berkefeld filter?

DR. ZINGHER: We used one specimen of bile that had been passed through the Berkefeld filter for most of our experimental work, as we wanted to avoid variations due to different specimens. However, we also used in some of our experiments fresh unfiltered bile with no difference in result. There is no statement in Besredka's communications whether or not he had passed the bile through a filter. In regard to Dr. Ewing's first question, this would no doubt be an interesting fact to determine. The point at issue however was the ultimate result, whether the rabbits did or did not develop an immunity when they were first prepared with bile and then given the killed vaccines by mouth. If results had been satisfactory, then a closer study of the pathology would have been made.

DR. HUNTOON: I would like to see the rabbits treated with calomel in place of the bile.

DR. JOBLING: I am afraid I do not understand just why you should attempt to remove the epithelium when you can give it intravenously.

DR. ZINGHER: Besredka states that the only immunizing effect after an intravenous injection of vaccine results from the small amount that actually comes in contact through the circulation with the intestinal wall. The administration of vaccine *per os* has ordinarily no immunizing effect, but by denuding the intestinal epithelium with bile Besredka believes that the vaccine is brought into intimate contact with the solitary lymph follicles of the intestinal wall, and this contact action produces an impermeability of the intestine to the living bacteria of their endo-toxin.

DR. HUNTOON: Besredka tried to prove that there is a difference between humoral and tissue immunity.

DR. ZINGHER: Besredka claims to have shown in his experiments that a general immunity as indicated by the presence of antibodies such as protective substances and agglutinins is of relatively little or no importance in protecting the individual against these intestinal infections. According to him, the local resistance of the intestinal wall is the most important factor. An interesting phase of intestinal immunity that develops during the latter part of the disease and during the early convalescence from the intestinal infections of the typhoid-dysentery group was recently discussed by Bordet before the Johns Hopkins Medical Society. I refer to the bacteriophage reaction of D'Herelle. According to D'Herelle we are dealing with a filterable virus which is present in the intestinal contents of patients suffering from various infections of the typhoid-dysentery group. This virus increases in amount as the patient progresses towards convalescence. A small amount of the Berkefeld filtrate of the stool which has been diluted with bouillon added to a fresh culture of the organism producing the infection will cause lysis and inhibition of the growth of the bacteria. When the bacteriophage is very active, the lytic broth culture planted on agar slants will show no growth. When less active there will be seen on the surface of the agar slant small circular depressed areas surrounded by a good growth of the culture of the organism. These depressions are supposed to be colonies of the invisible microbe. Bordet has obtained the same lytic exudate from the peritoneal cavity of guinea pigs which have been injected with a few doses of *B. coli*.

DR. CORNWALL: This is not exactly apropos of the discussion. We know of course that typhoid vaccine has not been successful in protecting individuals under all circumstances against typhoid fever. While in France I had an opportunity to observe a small typhoid epidemic of some twenty-two cases, six of whom died. They had all been immunized at varying times with U. S. Army vaccine. In all of the six cases the intestinal lesions extended high in the duodenum, being within six inches of the pylorus in two instances. The gross examination suggested a greater immunity in the upper intestines, as the lesions became more extensive in the lower intestines. In some instances the duodenal lesions were completely healed, presenting the typical shaven beard appearance. In all of these cases there was a definite interstitial pancreatitis. So far as any autopsies I have seen, or reports I have read, it is not my impression that interstitial pancreatitis is an ordi-

nary accompaniment of typhoid fever. These lesions extend much higher than the lesions of typhoid I have been accustomed to see in New York. The lesions in the upper intestines would seem to have been taken care of pretty well. One case that died showed that the lesions in the duodenum, jejunum, and upper ileum were all very well healed, and there were just two or three active lesions very low down. It looked as if the man should have gone on to convalescence. I should like to ask, if, in the experience of those present, interstitial pancreatitis has been observed as a frequent accompaniment of typhoid fever.

DR. ZINGER: Besredka's statement with regard to the incidence of typhoid fever in the French Army does not correspond entirely to the results published by Major Edouard Riis on the same subject. The latter showed that the incidence of typhoid and para-typhoid fever was considerable in the French Army during the first year of the war when the mobilization was so rapid that anti-typhoid vaccination could not be carried out. But just as soon as the French authorities started to vaccinate their troops with typhoid vaccine, the incidence of this disease was greatly diminished, while that of para-typhoid remained unchanged. The triple typhoid vaccine finally used consisting of typhoid and the para-typhoid strains reduced the incidence of these diseases in the French Army to a very low percentage. One must also remember our own experience with typhoid vaccination in the American Army. Some of the soldiers who developed typhoid later had received only an incomplete series of triple typhoid injections, or no vaccine at all. These soldiers in one way or another avoided the injection of the vaccine, and thought that they were getting the best of the Army surgeons.

QUIESCENT METASTATIC GASTRIC CARCINOMA

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New York City)*

This case is of interest from the standpoint of immunity in cancer.

The patient, a German, male, aged fifty-three, was admitted to the hospital complaining of weakness and fever. His past history was uneventful except for the fact that he very definitely asserted that ten years previously he had been operated upon for a malignant stenosis of the pylorus. He was in the hospital for a period of two months, eventually dying of pulmonary edema. Physical examination showed the following: a lemon yellow color, no cardiac murmur, evidences of a probably healed tuberculosis of both apices, and a slightly enlarged spleen. Two days before his death fluid was

demonstrable in both pleural cavities, and a sudden shower of petechiæ appeared on the abdomen and inner aspects of both forearms and thighs. The radiographic examination showed a patent gastroenterostomy, but gave no evidence of a pylorus or duodenal cap. His blood counts showed a leukopenia, with a slight lymphocytosis; his red cell count had all the characteristics of an anemia of the pernicious type. His urine showed a faint trace of albumin with an occasional cast. All other laboratory examinations were negative. During his stay in the hospital he had a fever of a septic type ranging between the normal and 103° F.

The cardinal points demonstrable at autopsy were a double sided hydrothorax, fresh small vegetations on the middle leaf of both the mitral and aortic valves, a healed and calcified tuberculosis involving both apices, parenchymatous degeneration of the liver, an acute splenic tumor with a recent infarct in the upper pole, and a mild degree of chronic nephritis.

The findings which are of interest in the present connection were those of the gastrointestinal tract. The pylorus and a portion of the descending duodenum were absent, and the stomach was bound to the liver by a band of dense adhesions. At about the middle of the stomach there was a posterior gastroenterostomy with the first portion of the jejunum. In the mesentery of the jejunum there were about thirty-five hard white nodules varying from 0.25 to 1 cm. in diameter. On section these masses were very firm and had the gross appearance of fibroids, and they were distinctly different in appearance from the pink soft mesenteric lymph glands. These

Quiescent carcinoma cells in liver.

masses on microscopical examination showed polymorphous cells with large nuclei and dense protoplasm arranged in a variety of ways, some being in broad sheets, others in strands, and still others in alveoli. Supporting these cells was a dense hyaline trabeculated connective tissue in which were collections of lymphoid cells having the architecture of lymph gland germinal centers. The condition is well shown in the accompanying photographs.

Several years ago in making a summary of the reported cases of spontaneous recession of human malignant tumors it was pointed out that such occurrences were not quite as rare as is commonly supposed. It is the experience of most surgeons and pathologists to have encountered cases of neoplasia in which there is a recrudescence at an unusually late interval, thus we have recently seen a breast carcinoma which developed a metastasis twenty-three years after the breast amputation. That neoplastic cells with their well-known power of almost limitless growth should remain quiescent for such long periods seems almost unbelievable, but as the present case shows such an occurrence is possible. The observation and recording of cases of this type are of extreme importance, for such cases demonstrate that at times

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Quiescent carcinoma nest in mesenteric lymph-node.

nature can control the process, and what nature can do, man will eventually be able to duplicate, even though the present outlook is pessimistic in the extreme. In conclusion we would urge the necessity for a very careful inspection of all cases coming to autopsy at any considerable period after the removal of a neoplasm, particularly where death has resulted from a noncancerous condition. An analysis of many cases of this type may possibly lead to therapeutic measures which will prove to be of great value.

Discussion:

DR. WOOD: I have seen a number of cases of carcinoma of the breast which after operation have had recurrence either in the scar or the supra-clavicular nodes at the end of from five to fifteen years, and in which the morphology of the tumor was that of the primary growth, as the original sections were in my collection at St. Luke's for comparison. This case of Dr. Rohdenburg's is however much more interesting than any of mine, because it is more exceptional, as the late recurrences of a breast carcinoma are well known. It is not necessary to speak of the folly of reporting cases of neoplasm as cured in six months before this audience and in the presence of this interesting report, yet the current literature is full of them. We have to be still more cautious with x-ray and radium reports, because all of our animal experiments show that the cells after large doses of radiation are slowed in their growth, and a tumor which would normally recur in one week does not return for six or seven weeks. This corresponds to years in man. That a similar slowing may occur in human material is shown by the fact that there have been a number of cases reported of recurrence eight or nine years after an apparent cure of the tumor by x-ray. One patient whom I saw went nine years without symptoms after treatment of an epithelioma of the lip, and then developed a recurrence in the neck, so that much discretion should be used in talking about the cure of a carcinoma.

METASTASIS OF CARCINOMA INTO AN ENDOTHELIOMA OF THE OPTIC SHEATH

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*Abstract*¹

History and Clinical Features: Mrs. J., aged 45, was admitted to Harlem Hospital on March 26, 1920, with a diagnosis of carcinoma of the brain. The left eye has been practically blind since about October, 1917. Vision in the right eye had been good until the last three months. The left breast had been removed for carcinoma in December, 1918. The important clinical features were: (1) practical loss of vision (light perception only) in the left eye, of long duration, associated with only moderate dilatation of the pupil, sluggish response to light, slight temporal pallor of the disc and absence of vascular changes in the retina; (2) temporal pallor of the left disc; and (3) unilateral papilloedema of the right disc with reduction of vision to perception of movement of fingers at one meter. The patient died eight days after admission.

Necropsy: This was limited to the cranium. The cerebral convolutions were flattened. Surrounding and adherent to the intra-cranial portion of the left optic nerve was a rounded tumor about 3 cm. in diameter. The left optic nerve was elongated and distorted by the tumor and the optic chiasm was displaced to the right. Cut surface of the tumor appeared white and homogeneous. Upon sectioning the brain several separate tumor nodules were found in various parts of its substance.

Microscopic Examination: Sections of the cerebral metastases show infiltrating new growth, consisting of large cells arranged in solid masses, as narrow columns and sometimes as tubules. The nuclei are large and mitotic figures are frequent. These tumors are regarded as secondary carcinomata from the primary growth in the breast.

Sections of the rounded tumor at the left optic foramen show a mixed character. In general it consists of irregular whorls of densely packed, elongated or spindle cells separated by somewhat looser connective tissue. Small hyaline bodies with concentric markings and deposits of lime salts are present in very small numbers. At one place the lumen of a large vein contains a mass of the new growth projecting from the wall into the lumen. These general features characterize the tumor as a dural endothelioma.

This new growth was readily separated from the neighboring structures, with the exception of the left optic nerve and its sheath. This nerve is

¹ The full paper, with illustrations, will appear in the *Archives of Ophthalmology*, 1921, Vol. 50, p. 128-136.

surrounded by the tumor at the inner termination of the optic foramen and considerably distorted. Sections show the intracanalicular portion of the intervaginal space occupied by the endothelioma, which does not pierce the pial sheath but appears continuous with the inner layer of the dural sheath and the outer layer of the pial sheath. The tumor has evidently taken origin from the layer of cells lining the intervaginal space in the intracanalicular portion of the optic sheath; it has compressed the nerve in this region and has extended backward in the intervaginal space to the cranial cavity, where it has enlarged to form the visible irregularly rounded mass in the sub-arachnoid space.

Mallory has somewhat recently studied the type cells of these tumors and he would place them in a new class designated as arachnoid fibroblastoma. He considers the lining of the sub-arachnoid space, from which these tumors are derived, to be merely a differentiated connective tissue, rather than endothelium.

Within the sections of this endothelioma (arachnoid fibroblastoma) are found groups of cells of a quite different type. These occur in the inferior and mesial portion of the tumor. They appear to correspond in all respects with the type of cell in the cerebral metastases and many of these cells show mitotic division figures. There is here, evidently, a metastatic carcinoma of recent development invading the basal portion of a dural endothelioma of longer standing.

Pathological alterations have not been demonstrated in the sections of the right optic nerve. The left optic nerve, on the other hand, was distorted and compressed near its entrance into the cranial cavity and the intervaginal space filled up with new growth in the inner half of the intracanalicular portion. This new growth is endothelioma containing nests of carcinoma. The cross section at the intracranial end of this nerve shows extensive degeneration of the nerve, doubtless brought about by the pressure upon the nerve within the optic foramen. Cross section of the nerve at the posterior orbital portion shows the myelin fairly well preserved for the most part, but there is a somewhat indefinitely outlined crescentic light patch of degeneration in the temporal half of the nerve, which evidently corresponds to the situation of the more delicate papillo-macular bundle of fibers.

Summary: The anatomical points of interest may be enumerated as follows: (1) multiple metastatic carcinoma of the cerebral substance; (2) large dural endothelioma (arachnoid fibroblastoma), arising in the intervaginal space in the intracanalicular portion of the left optic sheath, compressing and distorting the nerve and extending backward to expand into a large rounded

mass in the intracranial subarachnoid space; its pedicle and inferior portion being infiltrated also by metastatic carcinoma; (3) extensive degeneration of the intracranial portion of the left optic nerve associated with rather limited degeneration of the posterior orbital segment, the latter confined to the papillomacular region of the nerve.

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Discussion:

DR. LARKIN: In looking over the sections of the tumor I observed something that I have never seen before in a brain tumor. The tumor belongs to that type seen frequently in the meninges, single or multiple endothelioma. These tumors have a typical morphology and a typical histology. In looking over these sections there is evident a mixture with a different tumor type; there is carcinoma mixed with endothelioma. It is rather convincingly shown in sections given me that an endothelioma has metastasized into a blood vessel. This is worthy of note. There are three histological types of tumor in this brain; one is an endothelioma which is perfectly characteristic histologically; the other is an admixture of endothelioma with carcinoma, the carcinoma arising as a metastasis from the breast, and there is a different type of tumor which I do not believe Dr. MacNeal has shown on the slide. It is a peripheral arrangement of cells closely packed around the blood vessels scattered here and there in the brain substance, so that the pictures show an endothelioma, a carcinoma, and a whorl-like arrangement of an endothelioma.

DR. MACNEAL: If I understood Dr. Larkin correctly, he regards the material inside the blood vessels as a third type of tumor, or as indicating a tendency on the part of the cells of the endothelioma which is not commonly observed. The reports of this type of tumor are not very abundant, but the most careful study seems to be that of Mallory, and he calls attention to the fact that the cells of the arachnoid have a normal tendency to form groups of cells, which are anatomically known as arachnoid villi, which under normal conditions extend into the blood vessels. The extension of these cells into the blood vessel does not justify one in assuming that a metastasis is being set up, for we must remember that the structure resembles a perfectly normal structure. A tendency to produce structures similar to the normal is observed in many of the benign tumors. My interpretation here may of course be incorrect, but I would say that we have in this particular

picture something which resembles more or less accurately the formation of an arachnoidal villus growing into a vein. It does correspond very accurately indeed with a perfectly normal arachnoidal villus in a child five years old, as shown in one of the figures of Mallory's paper. I do not believe that you can assume that there is a metastasis here merely because of this villus growing into the vein. It would be necessary to demonstrate the presence of secondary tumors of this type separate from the primary endothelioma. I cannot convince myself that we have anything in the brain substance which corresponds to the arachnoid fibroblastoma (endothelioma). All the other tumors found in the pituitary body and in the brain substance seemed to correspond with the second type of tumor, the carcinoma, and not to the fibroblastoma or endothelioma. That is my interpretation of the thing.

DR. LARKIN: The histology of this tumor differs from the appearance which I have seen in other endotheliomata of the dura. There is no question as to the nature of the metastatic masses which point into the veins in different parts of the endothelial tumors. The histological type of metastasizing mass into the vein corresponds exactly to the type of tumor outside, that is, there are the whorls which are in the vein itself, and these whorls are similar to the cell type found outside the vein in the tumor itself. Mixed up in the mass of tumor tissue outside of the vein are secondary tumors derived from the carcinoma of the breast. I think this is an unusual picture of metastatic involvement so interesting histologically that it is worthy of record.

DR. MACNEAL: I am not sure yet that I comprehend the point Dr. Larkin has in mind. I agree perfectly that the villus is a growth inside the blood-vessel, and that it is similar in structure to the arachnoid fibroblastoma outside of the vessel in that particular tumor, but when you transfer your attention to the metastases I cannot see anything which corresponds to the arachnoid fibroblastoma. If there are sections showing this relationship I have not seen them, and I would be very glad to do so. I have not been able to find any such structure at a distance from the original large rounded tumor, and it seems to me that proof of metastasis must rest on such a finding.

DR. LARKIN: There is no question that we have two different types of tumors growing in the brain.

DR. MACNEAL: I have not been able to satisfy myself of that. The large tumor was not in the brain. It was in the sub-arachnoid space.

DR. LARKIN: I have some sections you gave me of two different types of tumor, one an endothelioma with an admixture of carcinoma, and another tumor which is perithelial in type. Histologically there is an endothelioma and a carcinoma, and another type of tumor which is not explainable.

DR. MACNEAL: In the brain substance we have not demonstrated this endothelioma. The only place we have been able to find it is in this one mass which was attached to the optic nerve and was growing freely in the sub-arachnoid space.

THE EXPERIMENTAL PRODUCTION OF SARCOMA OF THE LIVER OF RATS¹

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F. C. Wood, Director)

The relationship between chronic irritation and the appearance of neoplasms in man has long been recognized. The best known examples are the tumors following soot or tar irritation, the Bilharzia, kangri, and betel nut cancers, and the new growths observed in x-ray and anilin workers. While the early literature of experimental cancer contains accounts of successful results in arousing malignant transformation of tissues by various forms of irritation, most of these reports are unconvincing owing to doubtful histological proof and inadequate biological data, and the exact nature of the growths obtained remains obscure.

In recent years interest in this subject was revived by the experiments of Fischer,¹ who by the injection of Scharlach R. elicited lesions in the skin of rabbits histologically resembling cancer. These lesions and similar ones produced by other observers, however, never metastasized nor were transplantable and they disappeared as the irritating material was absorbed.

Clunet² was able to obtain one neoplasm in a rat after producing x-ray burns in a large number of animals. This tumor, a sarcoma, was transplanted and yielded one temporary growth which later disappeared completely. By the same method Marie, Clunet, and Raulot-La Pointe,³ produced a transplantable rat sarcoma. These experiments have been repeated on a large scale in the Crocker Laboratory on rats and rabbits but without the appearance of any tumors. Fibiger⁴ in 1914 published detailed reports of nineteen rats in which hyperplasias of the gastric mucosa resembling carcinomata resulted from feeding the animals with cockroaches infested with the nematode worm, *Spiroptera*.

¹ The authors published "A Preliminary Report on the Experimental Production of Sarcoma of the Liver of Rats," in *Proc. Soc. Exper. Biol. and Med.*, 1920, xviii, 29-30.

His subsequent investigations^{5, 6} increased the number of such hyperplasias to 84. In one group of rats of a particular inbred strain he obtained 54 tumors in the 134 animals which lived for 30 days or longer. In 8 of the 84 cases he observed lung metastases, thus proving that the tumors were biologically as well as morphologically, carcinoma. This investigator states: "*Spiroptera* cancer very exceptionally attains the stage of develop-

FIG. 1. Early spindle-cell tumor, IRS 8/o, shown in Fig. 5. $\times 400$.

ment distinguishable by macroscopic examination." He was unable to transplant these rat tumors, although he has recently reported⁷ a propagable spiroptera carcinoma of the mouse stomach which he has carried through four generations of mice. By employing the same agent and method Fibiger⁸ has produced

five epitheliomata of the tongue of rats, two of which showed metastatic deposits in the perineural lymph-spaces. Yamagiwa and Ichikawa^{9, 10} have announced the successful production of epithelioma of the ear of rabbits by painting the inner surface of the ear repeatedly with coal-tar. They report twelve cases of carcinoma, but without giving the total number of rabbits treated. Of these twelve tumors three showed lymph-node metastases.

FIG. 2. Early polymorphous-cell tumor, IRS 9/6, shown in Fig. 4. $\times 400$.

However, these authors did not succeed in their attempts to transplant the tumors. The experiments of Yamagiwa and Ichikawa were repeated on mice by Tsutsui¹¹ and more recently by Fibiger and Bang.¹² These investigators repeatedly painted the skin of the body of the mice with coal-tar. Of the 67 mice em-



ployed by Tsutsui which lived over 100 days, 16 developed carcinoma, and in two cases metastases were found in the lungs. Fibiger and Bang reported the development of 22 carcinomata and two carcinosarcomata in 26 mice which lived six months or longer. Of these tumors, 6 metastasized in the axillary lymph-nodes and 2 in the lungs, and 3 grew on transplantation.

FIG. 3. IRS 3/0, showing the mixed-cell type. $\times 400$.

Thus, so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable.

In previous papers from the Crocker Fund, Rohdenburg and Bullock^{13, 14, 15} reported twelve spontaneous sarcomata of the liver of rats arising in the walls of cysts of *Cysticercus fasciolaris*,

and described six of these growths in detail. Since the last publication eight additional spontaneous rat sarcomata of similar origin have been observed, making a total of 20 cases. Only two of these tumors were transplanted.¹⁵ One of these is now in the forty-sixth generation, the other was carried for over eleven months (14 generations), and then discarded. In the last of the publications referred to above, it was shown that of the thirty

FIG. 4. Low power of an early intracystic polymorphous-cell sarcoma.
IRS 9/o.

liver sarcomata of rats reported by other investigators, 90 per cent. were associated with the *Cysticercus fasciolaris*. Hirschfeld¹⁶ recently reported an additional case of angiosarcoma of the rat liver associated with this parasite and in concluding his article stated that feeding experiments are in progress having as their object the production of sarcoma. However, he left to the imagination of the reader the kind of material with which he fed

his animals, though the most probable inference from the context is that he employed the larvæ.

Infestation of the rat by *Cysticercus fasciolaris*, which is the larval stage of *Tenia crassicollis* of the cat, follows the ingestion by the rat of food contaminated with cat feces containing the eggs of this tapeworm. The outer membrane of the egg is

FIG. 5. Low power of IRS 8/0, showing nodules of spindle-cell sarcoma projecting into the cyst cavity.

digested away; and the onchosphere thus liberated penetrates a blood-vessel of the intestinal wall, and passes into the portal circulation, coming to rest in a capillary of the liver, where it begins its larval development. During the course of the second day

FIG. 6. IRS 19/o, from which a slice has been removed to expose the cyst cavity.

after feeding mice the eggs of this *Tenia*. Braun¹⁷ found the larvæ in the capillaries of the liver. After a series of reactions¹ in the tissues of the host which immediately surround the larva, there is gradually evolved a cyst wall of varying cellularity which encloses the parasite. Within the cyst the larva develops into a long, flattened segmented worm resembling an adult tape-

FIG. 7. IRS 16/0, showing infiltration of the liver by the tumor. $\times 400$.

worm, but without sexual differentiation. It lies free in the cyst cavity, bathed in a variable amount of thin, clear, straw-colored fluid. In many cases, through some influence of the worm, as yet undetermined, the cells of the cyst wall undergo active proliferation or even assume malignant properties.

¹ The histogenesis of the cyst will be considered in a subsequent report.

In March, 1917, Bullock and Rohdenburg attempted to induce sarcoma of the rat liver by employing *Cysticercus fasciolaris* as an agent. In that experiment 100 rats were fed with cat feces

FIG. 8. IRS 64/o, showing primary tumor and general peritoneal metastases. The cyst had been opened to expose the cavity and parasite.

containing the eggs of *Tenia crassicollis*. Unfortunately, these rats early succumbed to rat typhoid then epidemic in the labora-

tory, and the experiment was not resumed until the fall of 1919 when it was undertaken on a larger scale by the present authors.

In October, 1919, 1,165 rats of five different strains and of estimated ages varying from 2 to 9 months were fed with *Tenia* eggs from cat feces. The feces were obtained in a fresh state from a single cat. This material was mixed thoroughly with water, and squeezed through cheese-cloth, and the expressed fluid either was allowed to settle or was centrifuged. The sediment was mixed with water sufficient to reduce the number of eggs per drop to about 10 to 30. The rats were fed *per os* with a medicine dropper, each animal receiving one or two drops (about 10 to 60 eggs). Preceding the feeding of each rat, the suspension of eggs was actively agitated before it was drawn up into the dropper in order to approach uniformity in the number of eggs administered.

To determine whether or not the animals were infested with the parasite a few rats from each group were killed and examined at varying intervals. In all these animals the larvæ had reached the liver; but in one group, composed of a particular strain of animals several months older than the others, the larvæ failed to grow. Consequently the animals of this group, comprising 600 originally, were killed and autopsied five months after they were fed. The small percentage of animals showing growing larvæ demonstrated the economic wisdom of this sacrifice. Of the remaining animals 279 were alive July 29, 1920, the day before the first tumor was found. By January 18, 1921, 230 of these had either come to autopsy by death from natural causes or been killed for confirmation of a clinical diagnosis of tumor. Fifty-five of these bore tumors which were recognizable in the gross; that is, 29 per cent. of the dead animals which were infested with the parasite, or 20 per cent. of all the animals alive when the first tumor was found, have shown tumors. Forty-nine of the 279 are still under observation. About 2,500 descendants of the original animals have been added to the experiment. They represent four generations and are all of known ages; and a high percentage is fully pedigreed. Thirty of the first generation of these de-

scendants have thus far developed tumors. These with the fifty-five from the original stock make a total to date of 85 tumor-bearers.

These tumors belong to two histological types or to a mixture of these, being composed of either spindle or polymorphous cells, or containing both kinds in varying proportions (Figs. 1, 2, and 3).

FIG. 9. Omental metastases of a polymorphous-cell sarcoma, IRS 4/o, invading pancreas. $\times 400$.

Various stages of growth of these sarcomata are represented in the above series. The smaller tumors generally occurred as single or multiple localized nodules in the cyst wall which either encroached upon the cyst cavity or projected externally. They

involved either the inner or the outer zone of the cyst wall or its

FIG. 10. IRS 76/0, showing relatively small tumor and discrete and confluent secondary deposits on the surface of the liver.

entire thickness. Other small tumors appeared as diffuse thickenings of the cyst wall, which included a part or the entire area of

the cyst. Fig. 4 is a low power photomicrograph of a portion of a cyst wall containing the early polymorphous-cell tumor shown in Fig. 2. A cyst wall with nodules of pure spindle-cell sarcoma projecting into the cyst cavity is shown in Fig. 5. The high power appearance of one of these nodules is shown in Fig. 1.

FIG. 11. Embolus of a spindle-cell sarcoma, IRS 1/0, occupying a blood-vessel in the wall of a cyst $\times 400$.

The site or sites of origin of the tumor in the cyst wall and the direction and rate of tumor growth probably explain the position of the cyst in the larger tumors. It was either buried in the tumor substance, being centrally or eccentrically placed, or it was situated on the surface of the tumor, the free wall being generally completely transformed into sarcoma. Fig 6 shows a

photograph of a rat with a moderate sized tumor from which a slice has been removed in order to expose the cyst cavity. Sometimes, as in this case, the cavity remained large; but at other times it was partly or almost completely obliterated by the ingrowth of the surrounding tumor. Gross examination was sufficient to disclose the presence of a parasite in all but fourteen of the tumors.

FIG. 12. Tumor from the first transplantation of IRS 3/0. $\times 400$.

In seven of these cases there were cyst-like cavities in the tumors and free worms in the peritoneal cavities. Each of the other seven showed extensive necrosis, which may have destroyed and effaced both cyst and parasite. However, there is a possibility that the latter seven tumors originated in the liver outside the walls of the cysts, although early extracystic tumors have not

been observed. Besides the primary tumor cyst other cysts in the neighborhood were frequently involved by the extension of the growth. On the other hand, in a few instances two cysts were so placed in one tumor mass that the most probable inference was that they represented independent tumor foci, which later coalesced.

These induced sarcomata often grew very rapidly as was evidenced by a two or three fold increase in size in the course of a week or ten days, the tumor size being estimated by palpation. They sometimes replaced a large part of the liver substance and attained a size several times as great as that of the normal organ. Fig. 7 shows a photomicrograph of one of these tumors invading the surrounding liver. The neoplasms occurred in all parts of the liver, the percentage of tumors in any one lobe corresponding roughly to the proportionate size of the lobe. In the gross the tumors were either smooth or nodular, and often showed necrosis, associated with hemorrhage. They varied in consistency from firm and elastic to soft and brainlike, and were generally richly supplied with blood vessels.

Gross metastases were almost always associated with the larger tumors, and frequently occurred with tumors of intermediate sizes. In 52 of the 85 cases metastases were distinguishable in the gross. The smallest tumor in the series which showed macroscopic metastases measured 1.5 x 1.3 x 1 cm. The omental tissues were the most frequent site of secondary tumor deposits, and were often plastered to the surface of the tumor. Where metastasis was generalized, there was involvement of the omentum, the mesentery, the serous surfaces of the viscera, the diaphragm, and the abdominal wall.

Fig. 8 is a photograph of a specimen showing rather generalized metastases in the peritoneum. The secondary tumors sometimes infiltrated the organs upon which they rested (Fig. 9). Such metastatic tumors were frequent on the surface of the liver (Fig. 10), and were often found on the walls of other cysts. Not infrequently they invaded the muscles of the abdominal wall and diaphragm; and in a few cases, where the diaphragm was

penetrated by the growth, tumor nodules were observed on the pleura and pericardium, and in one instance there was invasion of the heart and lungs. These secondary tumors are probably often the result of implantation of tumor cells, but some are undoubtedly true metastases since tumor emboli have been demonstrated in the blood vessels. A sarcoma embolus is shown in Fig. 11.

FIG. 13. Tumor of the first transplantation of IRS 4/o. $\times 400$.

Most of these induced tumors which were transplanted into the subcutaneous tissues of rats showed a moderate to a high percentage of successful inoculations and many of the daughter tumors grew progressively and rapidly and maintained the morphological type of the original tumor. Figs. 12 and 13 show the

histological appearance of tumors of the first transplantation of IRS₃ and IRS₄, and should be compared with Figs. 3 and 9 respectively; and Figs. 16 and 17 should be compared with Fig.

FIG. 14. Transplanted tumor, IRS 3/1A, No 7, showing metastases in the neck and lungs.

15. Of the 43 thus tested only two failed to grow and two others were lost in the second generation. This high percentage of transplantability contrasts markedly with the few transplantable growths obtained by other methods and proves the malignant

nature of these sarcomata. Some of the transplanted tumors of certain strains showed a tendency to recede after growing progressively for varying periods of time; others continued to grow progressively and ultimately caused the death of the rats. Some of them reached enormous sizes, and in several cases the tumors

FIG. 15. Spindle-cell sarcoma, IRS 38/0. $\times 400$.

weighed more than their hosts. The first generation of transplants from each of 20 different induced sarcomata has been observed for a sufficiently long period to distinguish between progressively growing and receding tumors. The inoculation results varied from a single progressively growing tumor and twenty-five negative (IRS 7/1A), to twenty progressively growing and seven receding tumors (IRS 38/1A). In all twenty series 768 animals were

inoculated. Of these 363 were negative, 216 had receding tumors, and 189 had progressively growing tumors. That is, on an average the transplantation of one of these induced sarcoma resulted in 24.6 per cent. progressively growing tumors, 28.1 per cent. receding tumors, and 47.3 per cent. negatives. These percentages of successful inoculations are high compared with those usually obtained from the transplantation of spontaneous rat and

FIG. 16. Tumor from the first transplantation of IRS 38/o. $\times 400$.

mouse carcinomata. The recession of some of the tumors is quite characteristic of rat sarcomata in general. Lung metastases of the transplanted tumors of three different tumor strains have thus far been observed. One of these showed also a large secondary growth in the neck (Fig. 14). Photomicrographs of the primary

tumors, the transplanted tumor, and a lung metastasis of one of these strains are shown in Figs. 15, 16, and 17.

Some of the transplanted tumor strains were discarded after a few generations; others are still under observation and the first two which were transplanted are now in the sixth and fifth generation, respectively.

FIG. 17. Lung metastasis of the transplanted tumor shown in Fig. 16.
X 400.

All the tumor-bearing rats presented multiple cysts in the liver varying from 6 to 84 in number. In a high percentage of these animals only one of the cysts was primarily involved in the malignant process. In a few instances, however, two to four cysts, situated either close together or widely separated and in

different lobes of the liver, showed tumors of approximately the same size. In these cases metastases were not generalized and it seems probable that the tumors were of independent origin.

The tumor cysts contained larvæ the condition of which apparently depended upon the state of preservation of the cyst wall. When the cyst wall was partly uninvolved by the tumor, or consisted largely of healthy tumor tissue, the parasite was alive and intact, and measured from 15 to 38 cm. in length. These larvæ resembled the larvæ of the healthy uninvolved cysts. Where the transformed cyst wall was involved in the tumor necrosis the larva was usually dead, and distorted, and often necrotic and fragmented. It seems probable, therefore, that the live worm initiates the malignant process, and that the death of the worm is secondary to the growth and necrosis of the tumor.

The duration of the irritation necessary for the production of these tumors evidently varies within wide limits. A small but definite sarcoma was discovered as early as 248 days after the animal was fed cat feces. Recently, however, another rat has shown an early tumor 466 days after the ingestion of cat feces, and it is very probable that tumors will continue to appear in the 49 rats of the original group which are still under observation.

The tumor-bearing rats varied in age from 9½ to 18 months. Like a majority of the non-tumor-bearing animals which have come to autopsy, most of them were well nourished but showed no great excess of adipose tissue. On the other hand, tumors occasionally occurred in emaciated or in fat animals. Rats of both sexes and from each of the five strains tested were represented in the tumor series. Inspection of the data suggests that there is an age and probably also a strain difference in the susceptibility to infestation by the parasite, since young animals and certain strains seem to be most susceptible. Possibly there is also a strain difference in predisposition to the neoplastic conversion of the cyst. These and other similar problems can not be intelligently discussed until the rapidly accumulating data are analyzed.

Besides the 85 macroscopic tumors considered in the paper the histological material includes various stages in the malignant

transformation of the cyst wall and presents an unusual opportunity for the study of the histogenesis of these sarcomata.

Summary

1. Spindle and polymorphous-cell sarcomata have been induced in the livers of 85 rats through the mediation of the *Cysticercus fasciolaris*, the larval stage of the *Tenia crassicollis* of the cat.

2. Young rats of certain strains seemed to be most susceptible to the parasite.

3. Most of the tumors undoubtedly originated in the walls of parasitic cysts, and the others were probably of similar origin.

4. The duration of the irritation necessary for the production of tumors is evidently very variable, since one tumor was observed eight months after the animal had ingested the eggs, and a small tumor was lately found in an animal fifteen months after feeding.

5. The series represented all stages of tumor development from small single or multiple localized tumor nodules, or diffuse neoplastic areas in the cyst wall, to tumors which replace a large part of the liver and are several times the size of the normal organ.

6. The malignant nature of these tumors is evidenced by invasive growth, metastasis formation, and transplantability into other rats.

7. The invasive power is shown, not only by the primary induced tumors which early infiltrate the adjacent liver, but also by the metastatic tumors which often invade the organs upon which they rest.

8. The high percentage of transplantable tumors (90 per cent. of the 43 tested) is in sharp contrast with the few transplantable growths reported by other investigators.

9. The larvæ in the tumor cysts were usually alive and showed no apparent difference from the larvæ of other cysts not surrounded by tumor material. Dead larvæ were found in the tumor cysts only when tumor necrosis involved the cyst wall.

10. The tumor-bearing rats were 9½ to 18 months of age. They were of both sexes and of five strains.

11. This simple and practical method of inducing a high percentage yield of sarcomata in animals suitable for experimentation may be of service in several lines of cancer research including (1) the histogenesis and diagnosis of sarcoma, (2) the genetic behavior of immunity and predisposition factors, (3) prophylaxis, and (4) tumor therapy.

ADDENDA

From January 18, 1921, when this report was made, to May 7, 1921, cysticercus tumors developed in 125 additional rats in this experiment, making a total of 210 animals in which sarcomata have been experimentally produced.

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Discussion:

DR. EWING: This study is obviously of great interest and importance. It seems to me a parallel to Fibiger's results. The tumors seem to have

the biological characteristics which we are accustomed to insist on for a malignant process to a greater extent than Fibiger's did, although I feel that Fibiger's processes in all essential respects were experimentally produced carcinoma. One matter that interests me particularly is the histogenesis of the tumor. I would like to know what Dr. Wood thinks of the exact cell origin. Is it a type of reaction which can be compared with granulation tissue; where does it originate, and what is its significance? I think it might throw some light on the nature of this process if one could compare in the rat the connective tissue reactions to other irritants which do not go on to sarcoma. It may be that the rat's fibroblasts or epithelial cells or blood vessels respond to certain standard irritants much more actively than human tissues do, and if that is the case, then the significance of this sarcoma in the rat, while it is true sarcoma for the rat, may not have so direct a bearing on the study of sarcoma in man. I can well conceive that in such an animal as the rat connective tissue proliferation is very much more readily incited than it is in man, and that such processes as we would be inclined to regard as hypertrophic exuberant granulation tissue in man are comparable in the rat to a process which we call sarcoma. That will not alter at all the fact that this tumor is malignant for the rat.

Another point of interest concerns the question of morphological diagnosis of malignant tumors in man. Dr. Wood says that Fibiger went a little too far in attributing to some of his early proliferative processes the full significance of malignant tumors. I think that Dr. Wood and his associates are perhaps erring in the other direction.

In regard to the interpretation of these suspicious malignant-looking processes in man, I think they should be estimated from the clinical standpoint. They believe that the epithelial proliferations produced by various irritants are not true cancers, because they disappear when the irritant is removed, and consequently that similar malignant looking histological processes in man should not be regarded as cancer. I have observed the disappearance of seborrheic dermatitis of the lip after it had assumed some of the clinical characteristics of cancer and when it had probably reached a stage comparable to some of these experimental cancers. But the great majority of such lesions in man go on to develop cancer and from the clinical standpoint it is wise to regard them as early cancer. From that point of view all these observations confirm me in feeling that we must consider carcinoma not as a fully developed disease, but as a process which takes time and passes through stages of evolution, and that it is possible to recognize these stages and to determine by experience about what they are going to do. I am not inclined to think that the observations on experimental tumors or tumor-like processes in rats are apt to dislodge us from the position we hold in diagnosing these suspicious processes in man, for I shall continue to recognize as pre-cancerous or as early cancer the same processes in the breast which I have found heretofore suggested malignancy, in spite of the fact that many of these experimental processes disappear if the irritant is removed.

I have formed the impression that Drs. Rohdenburg and Bullock are a little less positive than they were originally. I think I recall a statement at one time by these authors casting aside the significance of the partially developed keratoses and downgrowths of epithelium, but in their last report I think I recall that they admitted that they had seen some of them go on and develop further phases of a true carcinoma in the clinical sense, even with the production of metastases. Whether they do admit it or not, it seems likely that they are producing carcinoma, and if they keep on long enough, they will get metastases. Dr. Wood gets his very easily. All these things are extremely important. They make one think about the conditions which surround the beginnings of cancer.

DR. LARKIN: I am interested in Dr. Wood's presentation, and the histological pictures have convinced me as to the nature of the tumor. Several of the slides show general widespread metastatic involvement in the omentum, lung, and elsewhere, and prove that the growths are malignant.

DR. ROHDENBURG: I think I can answer one of Dr. Ewing's questions. Owing to our inability to obtain access to the foreign literature during the war, we were not cognizant of the fact that Fibiger had been able to transplant his tumors, consequently one of our criticisms had already been answered, and of course falls. We did not have the opportunity until very recently of seeing Fibiger's slides. If you take some of his and put them beside ours, without seeing the labels, I doubt whether you could tell which was which. We have tried various ways of irritation in the rat liver. We have used pith balls and various other forms of irritation of solid and semi-solid characters, such as vaseline, and injected them directly into the liver. The connective tissue reaction was very different from that obtained in the wall of the cyst. Not all cysts, as Dr. Wood has said, become malignant. Those that do not become malignant are surrounded by hyaline connective tissue.

DR. EWING: Did you not conclude that your specimens which are identical with those of Fibiger are true carcinoma?

DR. ROHDENBURG: No, the lesions we were able to produce were not carcinomata; however, I believe that if we could keep up the irritation sufficiently long the lesions would become malignant. When you inject a solution of Scharlach R it is encapsulated by the epithelium, and it becomes impossible to duplicate mechanically what the cysticerci and the nematodes do naturally. I am willing to admit that if you could keep up the irritation it might become malignant. Our failure is not due to lack of patience as Ichikawa has insinuated,—it is due to the inability to reproduce the necessary mechanical conditions. Our irritation tumors have never formed metastases.

DR. EWING: May I ask the authors if they entertain any sympathy with Borrel's conception that in the case of those worms which produce malignant tumors there is a virus or a parasite in the worm which travels through to the cells which are invaded and thus produces a tumor as the direct result of the infection?

DR. ROHDENBURG: I do not. In the first place all the ova used in the experiments reported by Dr. Wood came from one cat. The cat feces were ground up and emulsified, centrifuged, and standardized as to ova to one drop. The rat is held; the mouth is opened, and one drop put down the pharynx. It would be logical to conclude that if one ovum were infected in Borrel's sense then all that group would be; therefore all cysts should produce tumors; while the developing cysts are multiple, the tumors are usually single.

DR. JOBLING: Were the tumors observed sufficiently early to determine if the growth developed from one point of the surrounding capsule, or if it was more general in origin?

DR. WOOD: To answer Dr. Jobling's question first: we got the tumors at varying stages, because it is not always possible to make an early diagnosis. Some of the early tumors which were obtained showed a considerable tumor on one side and a little one on the other. There were a number of very small tumors which started from one point in the capsule.

As to Dr. Ewing's question on the histogenesis of the tumor tissue, we are not prepared to answer that. It comes from the connective tissue of the liver, but we have not had time enough to study details as yet.

I was interested in hearing Dr. Ewing say that there are pre-cancerous phases when a tumor goes through a stage when it is not a tumor. It cannot be recognized microscopically when it is not malignant, but gradually shifts over to something that does not behave quite right, and then the vital question arises whether the growth is pre-cancerous or cancerous. That is just the point I was trying to make; for example, I have a series of slides from a case of x-ray dermatitis in which half of the tumor has been sectioned, and a number of pathologists have made a diagnosis of epithelioma, but the other half of the tumor spontaneously disappeared. A thing that disappears spontaneously can hardly be put into the class of malignant tumors. It is hard to tell whether many of the very early tumors on the hands and lips are going to be malignant a month from now, or whether they are malignant at the moment. Anyone who has seen Dr. Rohdenburg's slides of irritation growths would make a diagnosis of carcinoma morphologically. If you see gastric tubules extending down to the serosa of the stomach you are apt to make a diagnosis of carcinoma, but when after removal of the source of irritation from the rat's stomach the tumor disappears, it can hardly be called malignant. It is well to remember that the pathologist originally knew nothing about malignancy until the surgeon told him that a certain type of tumor recurred. That is the basis for malignancy. Anyone who looks at a cellular cystadenoma of the breast would assume that it was malignant from the morphology, but I have a collection of forty or fifty specimens which the average beginner would call malignant, and yet the tumor has never returned. In some of these the tumor was only partially excised, but there has been no recurrence. We must therefore believe that such suspicious tumors are clinically benign. I still stick to my point, and I believe that Dr. Ewing agrees with me, that there are tumors which from

the purely morphological point of view it is not always possible to designate as benign and malignant. The fibrosarcomata of the skin are a good example. As to these experimental tumors, and the question whether they are granulation tissue: they are not. They are definitely sarcoma. When there are metastases all over an animal the tissue is certainly not granulation tissue. When such tumors can be inoculated through five generations they are not composed of granulation tissue. I agree that a sarcoma in the rat is not a sarcoma in the human being. It is simply a peculiar type of tumor, and it is well known that rats are apt to have sarcomata and mice carcinomata. In dogs the tumors of the breast are carcinomata or sarcomata, and are not continuously transplantable. These are biological features showing how each animal has its own peculiar tumors.

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DR. DOUGLAS SYMMERS, *President*

THE BACTERIOPHAGE REACTION OF D'HÉRELLE

ABRAHAM ZINGHER, M.D.

The interesting studies published during the past three years by d'Hérelle,¹ Kabeshima,² Salimbeni,³ Bordet and Ciuca,⁴ Gratia,⁵ and Maisin⁶ have drawn our attention to an agent that seems to have an important function in the destruction of the intestinal bacteria and in the recovery from the diseases included in the typhoid-dysentery group. Such a bacteriophagic agent was originally described by Twort⁷ in the *Lancet*, 1915, in connection with observations on *staphylococcus* cultures derived from glycerinated vaccine virus, and on *coli* cultures from the intestinal tract of dogs suffering from distemper. Similar observations were also made by him on a large bacillus obtained from the intestinal tract of children suffering from diarrhoea.

The agent is described by d'Hérelle as a filterable virus which grows upon and destroys the pathogenic bacteria with which it is associated. It is found toward convalescence in the intestinal diseases, is not absolutely specific, and can be cultured indefinitely in series by transplanting a fraction of a loopful of the lytic fluid into fresh suspensions of the bacteria in bouillon.

These observations were first carried out by d'Hérelle in connection with the Shiga dysentery and then extended to the other types of dysentery, to typhoid, paratyphoid, and fowl typhoid.

Kabeshima does not consider this agent as a living virus, but as a ferment derived originally through the action of a leucocytic catalyzer upon the bacteria, causing the liberation of a ferment which can continue to act indefinitely in series of fresh suspensions of the organism.

Salimbeni's observations indicate that we are dealing with a myxameba-like organism which has two stages—a filterable spore stage and a vegetative fungus stage. These observations are probably erroneous. The appearances, which he describes, are probably artefacts developing during different stages of lysis of the bacteria.

More important, however, in explaining the nature of this agent is the work of Bordet and Ciuca, who consider that this lytic power is an hereditary lytic property produced by the action of leucocytic ferments upon bacteria, some of which subsequently acquire a property of being lytic for the original strain from which they were derived. Bordet and Ciuca obtained the lytic agent by the injection of a *B. coli* strain into the peritoneal cavity of guinea pigs. The action of this lytic peritoneal exudate upon the original strain showed up colonies of the *B. coli* which were resistant to lysis and very mucoid and translucent in appearance. The bacteria of this "modified" strain of *B. coli* were actively motile, resistant to the action of the lytic agent, and much more pathogenic for guinea pigs than the original strain. These "modified" bacteria have acquired the property of producing inhibition of growth and lysis of the original strain. This property is preserved through later generations and represents a new biological function of the bacteria.

One of Bordet's co-workers, Gratia, has shown more recently that in an old and evidently dead culture of the Bordet strain of *B. coli* small colonies were found that were markedly resistant to ageing. Upon transplantation these colonies proved to have the same resistant properties to the lytic agent as those of the resistant strain obtained directly by the action of the lytic fluid upon the original strain of *B. coli*. These studies, according to Gratia, seem to have an important bearing upon the questions of virulence, the heredity of acquired characteristics, and the formation of new races.

Through the kindness of Dr. Hardé, who brought specimens of lytic fluid from d'Hérelle to this country and placed them at my disposal, I was able to make some studies on the nature of this agent. The pressure of other work has prevented me from continuing these most interesting studies, and I can only submit the following limited observations:

One specimen marked "Bacteriophage anti-Shiga," dated May 19, 1919, produced inhibition of growth in a fresh suspension of the Shiga bacillus and caused lysis of bouillon cultures grown

24 to 48 hours. Subcultures were sterile. A trace of this new lytic fluid showed the same property toward fresh bouillon suspensions, which in turn exerted the same powerful lytic action, which could be continued on indefinitely in series.

By great dilution the action of this lytic agent was diminished. In place of the complete inhibition of growth on the agar subcultures which were made immediately after the addition of the diluted lytic fluid to a fresh suspension of *B. Shiga*, a surface growth developed which showed here and there circular depressions with no growth surrounded by a halo leading off into the growth. These circular depressions were considered by d'Hérèlle as representing colonies of the bacteriophage, by Gratia as the evidence of the lytic action of products of the resistant bacteria upon the non-resistant bacteria.

By making agar plates of the Shiga bacillus and streaking the surface crosswise with a loopful of the lytic fluid I could observe the following day a complete area of clearing along the path of the streaked lytic fluid which was surrounded by a regular surface culture of the Shiga bacillus. Studying the margin of the clear area, I noticed that the culture of the Shiga bacillus had at this point a shelving edge where it was quite translucent, and which upon microscopical examination showed the presence of most interesting structures. There was first a fine granular background, representing probably detritus derived from the bacteria; second, long, slender, refractive crystals, singly or in small groups of two and three; third, numerous irregular structures, not motile, pentagonal or hexagonal in shape, or of an irregular round form, which stood out clearly against the granular background. These bodies resemble closely in size and appearance crenated red blood cells. They could be floated in a hanging drop and seemed to have a somewhat spherical shape. They could be stained with Giemsa and less clearly with Gram's stain in ordinary preparations and in preparations made by impression from the agar plate. In the stained preparations the structures appeared as amorphous non-nucleated masses. It is probable that these structures represent *hyaline masses of protoplasm* resulting

from the action of the lytic agent upon the bacteria. Here and there along the margin of the streak small circular indentations could be seen in the culture proper which corresponded closely in appearance to the colonies of bacteriophage described by d'Hérelle. The microscopical examination of the margins of the circular areas showed numerous structures similar to those described above—granular detritus, refractive, slender crystals, and irregular protoplasmic hyaline bodies. The more central part of the clear streaked area showed in places upon microscopical examination similar structures.

After two to three days there appeared in the clear area small colonies which upon transplantation grew with difficulty. On the agar plates the subcultures of these resistant colonies did not show the above-described structures which indicate the action of the lytic agent upon non-resistant bacteria.

The specificity of the lytic fluid was also studied. It was found to completely inhibit a second strain and only partly inhibit a third strain of *B. Shiga*, and to produce complete inhibition of a Flexner-Harris and a Mt. Desert strain of dysentery bacilli. It had no action upon a typhoid strain (Pfeiffer), *B. coli*, *B. sanguinarium*, and paratyphoid A and B.

Microscopical studies of hanging drops made according to the method described by Salimbeni gave no evidence that we are dealing with a myxameba. The irregular hyaline structures described previously showed no motility. The lytic agent was found to produce very active and almost instantaneous agglutination of bacteria.

The lytic agent resists the temperature of 70° C. for one half hour, but is partly destroyed by a temperature of 75° C. for one half hour.

Studies were also made with the anti-typhoid bacteriophage sent over by d'Hérelle. On the agar plates inoculated with the *B. typhosus* (Pfeiffer) and streaked crosswise with a loopful of the lytic fluid, structures similar to those described above were found along the margin of the culture and within the cleared area.

The anti-typhoid lytic fluid produced complete inhibition and

lysis of the *B. typhosus* (Pfeiffer). It also produced complete inhibition and lysis of the Flexner-Harris and Shiga dysentery strain, but only partial inhibition and lysis of paratyphoid A and B strains, of five recently isolated typhoid strains, and of the Mt. Desert strain, and no lysis of the *B. coli* and *B. sanguinarium* strains.

A third bacteriophage against the *B. sanguinarium* was also studied. Structures similar to those described in connection with the anti-Shiga and anti-typhoid bacteriophage were also seen on plates inoculated with the *B. sanguinarium* and streaked crosswise with a loopful of the anti-sanguinarium lytic fluid. The lytic agent produced complete inhibition and lysis of three different strains of *B. sanguinarium*, of the Shiga strain, and of the typhoid (Pfeiffer) strain.

The foregoing short studies indicate that these lytic agents are not *absolutely specific* for their own bacterial strains. They also indicate that we can recognize the *lytic action* of these agents upon bacteria by the *curious irregular but sharply defined and prominent structures which are found on agar plates at the point of contact of the lytic agent and the bacterial culture—long, slender crystals and protoplasmic hyaline bodies*. A few small colonies developed slowly within the clear area on the streaked agar plates. Subcultures on agar showed that they were *resistant* to the action of the lytic agent. This was also seen when the lytic agent was added to fresh suspensions of these bacteria.

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Discussion:

DR. WILLIAMS: I have followed Dr. Zingher's work with a great deal of interest. The macroscopic appearance in these plates of rounded chewed-out areas is very similar to the appearance that can be obtained when inoculating amebas with cultures of suitable bacteria, such as *B. dysenteriae* or *B. typhi*. But under the microscope these appearances are nothing like those of any amebas I have ever seen. These small ameboid-like bodies look much more to me like broken down products than like living organisms.

DR. PARK: This paper deals with a subject which is both most interesting and most difficult of understanding. I think it must appear to all of us that it is almost impossible to conceive that the results are due to ferments alone since we do not know anything about a ferment which may increase. Again the idea that a microorganism would suddenly so change its function as to make a ferment which would attack the strain from which it had lately developed is something that we have never come across, so that naturally the newest hypothesis of Salimbeni that there is a parasite growing on the organism appealed very much to us. This theory has its own difficulties. If the parasitic fungi exist there must be a number of these. We are exploring in a new field which is very interesting. It is hazardous at the moment to say more than that.

MISS KUTTNER: I have been able to isolate a lytic principle similar to that described by d'Hérelle from a typhoid stool sent to me through the courtesy of the Health Department. It corresponds to practically everything d'Hérelle has described. It is non-specific; it acts on the homologous typhoid strain and on the other typhoid strains, as well as on Shiga and Mr. Desert dysentery bacilli. It has no action against paratyphoid A or B, or against *B. coli*. It is both inhibitory and lytic. I have not found that cultures dissolved or inhibited by this lytic principle remain sterile indefinitely as described by d'Hérelle. If cultures which have been acted upon by the lytic principle are plated after several days two types of colonies develop, one the typical round typhoid colony, the other irregular. The irregular colonies are often quite jagged and triangular, and if transplanted into broth do not make the broth turbid, whereas a normal colony from the same plate does, and furthermore, the lytic principle is also transmissible from one of these colonies fished into broth, that is, starting with a fishing of one of these triangular colonies in broth, the lytic principle can be transmitted in series in the same way as from the original stool filtrate. I would like to ask Dr. Zingher how he reconciles the theory of the ultra-microscopic spore with the fact that a single brief contact with this lytic principle changes the organism so as to give two types of colonies from one of which it is possible to transmit the lytic principle in series. For instance, if a small amount of the lytic principle I have isolated from a typhoid stool is added to a young turbid broth culture of typhoid, Shiga or Mt. Desert, and sub-cultures are immediately made, it will often be found that the two types of colonies, the normal and the lytic, will be obtained. I cannot understand how a single short contact with the lytic principle in this

way, which produces such an immediate and profound change in the cultures of three different organisms such as typhoid, Shiga and Mt. Desert, can be attributed to the action of a fungus.

DR. JOBLING: It is difficult to assign the phenomena described by Dr. Zingher to the action of either bacteria, fungi, or antibodies. The fact that Bordet was able to obtain a similar agent from bacteria after their injection into the peritoneal cavity of a guinea-pig complicates matters. Is the agent producing the lysis a normal inhabitant of the peritoneal cavity, or was Bordet fortunate in his choice of a guinea-pig? Are we to assume that there is in the intestine a specific substance, or organism, for each type of bacillus; or are we to believe that the agent exists free in the intestine, with the ability to become attached to any organism after which it cannot grow except in symbiosis with that particular organism?

DR. ZINGHER: I have not been able to confirm the observation of Salimbeni as regards the myxameba-like structures which he has observed in wet slide preparations of bacterial suspension and lytic agent. The small, highly refractile bodies which he describes in hanging drops of a freshly made preparation of bacteria and lytic agent seem to be simply the ends of bacteria, which are seen in a vertical instead of a horizontal position. I have noted the two types of colonies of which Miss Kuttner spoke. The irregular colonies show upon microscopic study the structures characteristic of the action of the lytic agent upon the bacteria—the long slender crystals and the sharply defined irregular hyaline masses.

CUTANEOUS REACTIONS IN HUMAN HYPER-SENSITIVENESS

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The two main points that I shall discuss with you regarding the cutaneous reaction in human hypersensitiveness are first the method of making the test and secondly the significance of the local reaction.

1. *Method of Testing:* Cutaneous tests can be made by the abrasion method when the substance to be tested is applied in dry form or as an extract, or by the intradermal method when a solution or extract is introduced into the skin by means of a fine hypodermic needle.

Dr. Brown has been making some very careful duplicate tests with these two methods in our clinic, and since time will not permit a detailed statement, I shall only say that the results warrant the conclusion that the intradermal test is by far the more delicate and gives definite positive results to agents definitely proven to be productive of clinical symptoms when the abrasion test, using these same agents, is absolutely negative. What follows has to do entirely with results from the use of the intradermal test and our own preparations.

2. *Significance of the Cutaneous Reaction:* The *local reaction* divides itself into three groups, (1) the immediate reaction, (2) delayed reaction, (3) negative. The *immediate reactions* are marked, moderate or slight. Marked reactions are characterized by the appearance of an urticarial wheal with pseudopod projections and a surrounding zone of hyperemia, appearing in ten to fifteen minutes. Moderate reactions lack the pseudopod projections and do not form so large a wheal. They have a hyperemic zone. The slight reactions show a hyperemic zone with little or no increase in the wheal. Slight and moderate reactions are at times obtained to extracts in a very weak solution and become marked where more concentrated solutions are tried. Where reactions are slight or moderate to the concentrated extracts they are dismissed as of no clinical significance unless they go on to develop delayed reactions and fall then into a different group to be discussed later.

Marked reactions are of the greatest importance, but they, too, are occasionally false. At times one gets what we call the "splash" reaction, when the point of the needle happens to lie between two easily separated layers of the derma or epiderma, and the extract seems to splash out at once into an area with irregular edges. In such cases the wheal looks like a marked positive reaction, but it lacks the hyperemic zone. This also happens when an air bubble is introduced by mistake. Then occasionally, but not frequently, a definite marked positive reaction is obtained, which can never be verified. These, too, must be set aside as of no clinical significance, for they could only indicate a

short fleeting phase of allergy, a clinical condition of which we are not as yet cognizant. But marked positive reactions occurring on repeated testings always indicate a true hypersensitiveness. This statement requires a reservation, or more truly an explanation, in order not to be misleading. Cutaneous hypersensitiveness does not necessarily indicate clinical hypersensitiveness, because in the ordinary course of life the allergen can never be brought in contact with the hypersensitive cells. Let me cite briefly two actual cases to illustrate the point:

The first is the case of a man forty-five years old who had been troubled for five years with a very extreme degree of vasomotor rhinitis, so-called. He gave marked cutaneous, ophthalmic and nasal reactions to corn and cottonseed meal. On the strength of this reaction one might have been tempted to withdraw corn and cornmeal from his diet. But it so happened that five years before this man had retired to a little farm and took great pride in his chickens which he fed himself religiously twice a day with corn and cottonseed meal. As soon as he stopped this his vasomotor rhinitis stopped. He was able to eat corn and cornmeal which he did freely as a test without the slightest trouble. An injection of extract of corn produced a constitutional reaction with coryza and cutaneous hyperemia and urticaria. This case also illustrates the dangers in the interpretation of positive reactions when applied to foods.

The other case is that of a woman thirty years of age who had never had hay fever of the early type, in May and June, and would have recognized it before because she had autumnal hay fever for about fifteen years. The test with a timothy pollen extract in March was markedly positive. That following June she had perfectly typical clinical hay fever of the early type.

We now have records of several such cases giving marked positive cutaneous reactions with negative ophthalmic reactions. Such cases we consider as potential hay-fever cases. They have no clinical symptoms because the mucous membranes have not become hypersensitive. But we have had the satisfaction of watching such cases develop clinical hay fever at a later date, at which time the mucous membranes react positively. Aside from the inheritance factor, such an experience tends to make one feel that the constitutional reaction is developed within the body by some means other than ordinary immunological procedure adopted in animal anaphylaxis.

Delayed cutaneous reactions occur from six to twenty-four hours after the test and are characterized by an area of edema and redness, usually with itching, sometimes only an inch or two in diameter, and at others extending to the elbow or even wrist when injection is made in the upper third of the arm. Of the clinical significance of such reactions nothing definite can be said at the present time. They are usually obtained with the food extracts rather than pollen extracts, and may occur in apparently normal individuals or in those with clinical asthma, urticaria or angio-neurotic edema; but so far as we can determine, foods giving such reactions may be eaten with impunity. We have never yet been able to make and prove a diagnosis on the basis of a delayed reaction, no matter how severe.

Negative Reactions: At the site of the test there is no enlargement of the papule caused by the injection of the 1/50–1/100 c.c. of the extract tested. There is no hyperemia or other evidence of cellular or vascular activity either immediate or delayed. In general such tests indicate absence of hypersensitiveness, at least in the skin. But in exceptional cases negative reactions occur when the clinical history is absolute and definite. We have seen a number of cases with a history of acute and severe abdominal pain, vomiting and diarrhoea, occurring about twenty minutes after the ingestion of clam. It has occurred not once, but several times. The cutaneous reaction is always negative. Such cases can readily be explained on the basis of a localization of the hypersensitive area to the gastric or upper intestinal tract. We have observed this same localization of hypersensitiveness to the nasal mucous membrane in a very few cases of vasomotor rhinitis, and not infrequently in hay fever the degree of hypersensitiveness is much greater in one eye than in the other.

Just as we see local reactions of the immediate and delayed type, so also do we see immediate and delayed clinical reactions. By delayed clinical reactions I mean a reaction occurring twenty-four hours to five days after the ingestion of a substance. Immediate local reactions, when they signify anything at all, indicate an immediate clinical reaction, but delayed local reactions are

not indicative of delayed clinical reactions; in fact, they have no known significance.

Time has not permitted me to go extensively into details nor to give statistics on the relative frequency of the exceptions to the rule. Suffice it to say that the application of the test to the diagnosis of clinical condition must be made with the greatest care, and we make it a rule for the absolute diagnosis of a specific etiologic factor to conform to the following commonsense requirements, which we have dignified by the term postulates:

1. Hypersensitiveness must be proven either by:

- (a) A local reaction of a marked type that can be verified at will, or by

- (b) A constitutional reaction that duplicates the clinical condition under study when the allergen is introduced by ingestion, inhalation, or by intradermal, subcutaneous, or intravenous injection.

2. It must be proven that the individual comes in contact with the reacting substance in such a way that it can be responsible for the clinical condition.

Dr. George M. Mackenzie read a paper entitled "The Relation of Antigen and Antibody to Serum Disease Susceptibility and Insusceptibility," which appeared in *The Journal of Experimental Medicine*, 1921, xxxiii.

Discussion:

DR. LONGCOPE: I have naturally been very much interested in this work of Dr. MacKenzie's. Serum disease, which is really a characteristic example of an acute infectious disease, offers a beautiful opportunity to study certain phases of the relationship of an infecting agent to antibody formation in a condition where the cause of the disease is not a living agent, but one with physical properties only. For protein is not a living agent. The experiments which Dr. MacKenzie has described I think offer very good evidence that there is an essential difference between the susceptible individual and the insusceptible individual to this disease produced by the non-viable substance, horse-serum—that the susceptible individual does readily produce antibodies and precipitins, whereas the insusceptible individuals are not likely to produce antibodies, while in them the antigen, the horse-serum, continues to circulate as a perfectly innocuous substance for long periods of

time. Dr. MacKenzie has discussed the possible explanation for these phenomena. I do not think there is any evidence to show that one explanation is better than another, but any observations or any data that can be brought to bear on the subject of individual susceptibility to disease are most important, and for that particular reason possible analogies are interesting, though it may not be proper to draw analogies for acute infectious diseases from these experiments.

In regard to Dr. Cooke's interesting observations, I am sure that Dr. MacKenzie has noticed that the intradermal tests were much more delicate than the dermal tests. Walker has ruled out the intradermal test, saying that it is difficult to read. I do not believe that there is any great difficulty in this regard, if the tests can be done with materials that are sufficiently diluted.

Dr. Cooke's observations on the reactions in the skin and in the mucous membranes, and their variation in the same individual to the same substance, are very interesting. We have noticed this a number of times, and I recall one man in particular who gave skin reactions to a great variety of substances. He was perfectly well when he was in the hospital, but whenever he left the hospital he was likely in a short time to have such a violent attack of asthma that he would be picked up in the street and taken to the accident ward of a hospital as a medical emergency. Among other things he gave a marked reaction to rabbits' serum, though he was perfectly certain that no animal ever gave him attacks of asthma. He said he could pet a rabbit and do anything he wanted to with it without danger of asthma. We took him into a room where a rabbit was. He touched the rabbit with his hand. Almost immediately he had an urticaria of the hand, and for a week subsequently he suffered from a terrific attack of asthma. Though he gave the same skin reaction to various other animal sera, he could be fed enormous quantities of dried serum without any disturbance whatsoever.

Another interesting thing is the varying degree of hypersensitiveness which great groups of individuals show. I have no doubt that if one selected a hundred or a thousand perfectly normal individuals that a good many of them would either give delayed or immediate reactions to certain protein substances. I give reactions to a certain number, and I have never had any symptoms from eating or coming in contact with any of these materials. There must be a variation in groups of individuals from those who are hypersensitive and who have symptoms which can be accounted for by this curious condition, through individuals who are rarely affected and finally to individuals who are perfectly normal, though still presenting evidences of hypersensitiveness when tested appropriately.

A confusing thing in interpreting the skin reaction is the frequency of multiple reactions. People who do have urticaria, asthma, etc., may react to a long series of substances, and we have seen a number of individuals who give extremely marked reactions to extracts of animal hairs, and yet in whom it is evident that the asthma is not brought on by inhalation of dust from these animals. I recall one boy in particular. From the strongly positive test we assumed that it was due to contact with some

animal, until we discovered from his mother that she thought eggs had something to do with it. He gave no reaction to eggs, by the ordinary tests, but when given large quantities of egg intradermally, he did give a fairly marked reaction to it, and when eggs were removed from his diet, he recovered and has remained perfectly well for several years, except for one or two attacks following the ingestion of eggs. This is simply an illustration of the difficulty of analyzing the significance of skin reactions when many positive tests are obtained.

DR. HUNTOON: I think from Dr. MacKenzie's paper that he does not make a distinction in classification between those people who give immediate reactions, and who give typical serum disease which comes on five to twelve days after the injection of the serum. I believe he stated that the hypersensitive cases stood at one end of the line, and the cases that give no reaction at all at the other, and there are all gradations in between. If this hypothesis is true that these two classes of symptoms belong in the same class, then these individuals should show a considerable amount of precipitin in their blood before the serum is injected, and in that event the cases that give extensive immediate reactions with small amounts of serum would later show a typical serum disease. I wish Dr. MacKenzie would inform me on these points.

DR. PARK: I was going to ask Dr. MacKenzie concerning the point brought up by Dr. Huntoon. Dr. Cooke's observations seemed to indicate a difference in significance between the early and late reactions, while those of Dr. MacKenzie seemed to class them together. His observations are of great interest and value, even if his interpretation of their meaning may later have to be modified. Dr. MacKenzie attributes the serum reaction largely to the patient's characteristics. I wonder how he explains the differences in the sera from different horses. Most sera used in treatment are mixtures from different horses. In order to estimate the individual characteristics we used individual horse serums and found the serum from some horses gave very different reactions from that from others. I remember that No. 83 gave about sixty per cent. of scarlatiniform reactions and had to be discarded. There is certainly a marked difference in the sera as well as in the patients. Realizing that proteins giving the therapeutic effects were not necessarily deleterious, we tried to modify or select the serum so as to avoid the unnecessary reactions such as the immediate chill following an intravenous injection. We have met with some peculiar as well as interesting results. We found for instance that we had a slightly turbid anti-toxin globular preparation which gave chills in about twenty-five per cent. of the cases injected. We filtered this and while perfectly clear it gave no chills, so we thought that by chance we had come upon the explanation. The next slightly turbid preparation we treated the same way, but without preventing the chills. What was more peculiar was that the good preparation was mixed serum from horses A and B, and the poor preparation was from horse B only. We now have a preparation which has become hazy and yet produces no chills, so that we see there is an unknown factor in the serum as well as in the patient, and that substances in one serum may

inhibit the action of those in another. I believe there must be a difference between what causes a delayed and an immediate reaction.

MRS. PARKER: In regard to Dr. Cooke's observation that he and Dr. Coca were not able to prove that pollen is antigenic, I wish to say that I have been able to show that alkaline extracts of ragweed pollen have definite antigenic properties as shown by the Dale method. At the present time I am sensitizing a series of guinea pigs in order to determine whether they can be made generally anaphylactic to pollen. Since the Dale method is the more delicate test and since it proves that pollen is antigenic I thought it worth while to report the fact that I have obtained positive results with this method.

DR. BERGER: Is it possible by means of the skin test to tell whether a patient is partially or to a marked degree desensitized after treatment with pollen extract or any antigen? Dr. Schloss reported a series of cases last June in which he fed egg-white to infants. If the patient developed urticaria following the ingestion of egg-white he noticed that while the urticaria was present the skin test was negative or reduced. He reported several cases where the skin reaction was markedly reduced during an attack of asthma. Is the skin sensitive to bacteria? If the patient has accompanying his asthma a bacterial infection of the chest would the skin be an index of sensitiveness to the bacteria? I would like to know if the various bacterial extracts which are on the market are of any value. The difficulty I have found with the intradermal method is to get an extract of horse dander or cat hair into solution. You can obtain a dehydrated product which comes in solid form and which has to be diluted with sodium hydroxide and subsequently neutralized with acid. I wonder whether that product is the one Dr. Cooke used, or did he use a suspension of the dander in saline or water.

DR. MACKENZIE: In regard to the question raised by Dr. Huntoon, I evidently did not make myself clear that at the time the serum was administered to these patients only one was hypersensitive to horse serum. All the others were normal people with negative skin reactions. Last year before this Society I showed the curves of antigen and antibody in the circulation for the individual who was hypersensitive at the time serum was administered. He showed immediate and accelerated reactions. In him the antibody production was also earlier. He had not only an accelerated symptomatic reaction, but an accelerated antibody formation. All the other individuals in this series were not hypersensitive to horse serum at the time it was first administered. The susceptibility refers to the susceptibility to serum disease.

As to the error in technique, I did not wish to take up much time in the paper to speak of it. In one individual there was a severe serum reaction and a high titer of precipitin. If he had conformed with the other members of the series, the precipitinogen should have disappeared with the rise of the precipitin to a high titer, but it did not. That patient was studied before we realized the importance of testing the anti-horse serum for traces of antigen, and it was possible that the patient's serum containing an abundance of antibody was precipitating traces of antigen in the anti-horse rabbit serum we were using.

As to the differences in sera which Dr. Park spoke of, I cannot say anything with accuracy on that, because I have not tabulated the cases according to what serum was used in any particular individual, but we have used only serum from the Rockefeller Institute and from the Department of Health. I am not sure just how many cases in the series were treated with one or the other serum.

DR. COOKE: In reference to Dr. MacKenzie's paper, I would like to say that if he can throw any light on the question of serum disease it is going to be a great help in the study of these delayed clinical reactions we see to-day.

I am also interested to know from Mrs. Parker that she has been able to demonstrate the antigenic properties of the pollen extract. Experiments of Coca, Flood and myself two years ago failed to show any antibody formation to ragweed pollen extract by the usual guinea-pig experiment.

There were a few questions as regards desensitization. When one injects hay fever patients with pollen extracts there is a decrease in the sensitiveness of the mucous membrane, but very little difference in the intradermal reaction. If there is any difference in the cutaneous reaction at all there is a tendency to disappearance of the itching which is usually a very marked manifestation of the reaction.

In the case of allergic children one has to be very careful in making any statement that what is being done in the way of injection or feeding has any effect on the course of the disease, because there is a tendency in all children to lose, naturally, the hypersensitive reaction to foods when this hypersensitiveness existed early in life, for in such cases it usually disappears from the eighth to the tenth year, at which time, although cutaneous reactions may or may not be present, the clinical reaction on the ingestion of the particular food has entirely disappeared. This is not due to any treatment. It is not due to injections or to feeding, because most of these children lose their hypersensitiveness when the specific food has never been eaten or injected. It is a natural phenomenon.

With regard to the bacterial proteins and sensitization, it is very difficult to say much. So far, using solutions of various bacterial proteins, we have never yet been able to get an immediate marked positive reaction that looked at all like the immediate reactions one gets with foods and pollen extracts, and furthermore, such reactions as do occur do not correspond to the bacteria that are isolated from the bronchial tract or from the nasopharynx. The whole question of bacterial hypersensitiveness is one about which we know very little at the present time.

There was one other question about the preparation of the extracts we used. One must always bear in mind that these reactions of necessity take place from some readily absorbable substance. It must be dissolved in the tears, or in the saliva, and be readily absorbable in order to get into contact with the cells. This being so, it is perfectly evident that when one speaks of getting reactions to cat hair or dog hair it is absolutely a misconception. What you do get reactions to are the epithelial cells that are attached, and the hair has nothing to do with the reaction at all. Solutions

of dander of animals are readily obtained, and there is no trouble at all about dealing with an insoluble substance.

DIFFUSE ENDOTHELIOMA OF BONE

JAMES EWING, M.D.

For some years I have been encountering in material curetted from bone tumors a structure which differed markedly from that of osteogenic sarcoma, was not identical with any known form of myeloma, and which had to be designated by the vague term "round cell sarcoma" of unknown origin and nature. I had no opportunity of following the course or learning the outcome of these cases, as most of them were treated by amputation of the limb.

Recently a case came under observation at the Memorial Hospital which revealed that this tumor is highly susceptible to radium, a fact that convinced me that the disease was entirely different from osteogenic sarcoma, which resists treatment by the physical agents.

The story of this case is briefly as follows:

A fourteen-year-old girl had been treated by an outside physician in 1918 for nasal discharge and occasional bleeding. Some ocular symptoms led to the suggestion of congenital lues, and a Wassermann reaction being weakly positive, salvarsan was administered. In November, 1918, while pulling on a rope, a spontaneous fracture of the ulna occurred, followed by swelling which gradually subsided. In January, 1919, the swelling recurred and continued with pain and disability until a well-marked tumor occupied the upper part of the arm. This tumor was noted to fluctuate in size. The veins of the skin were dilated, and the appearance led to the diagnosis of osteogenic sarcoma. Eight injections of Coley's toxins were administered at Mount Sinai Hospital, without notable effect.

On April twelfth at the Memorial Hospital a radium pack of 12,760 millicurie hours was applied to the arm, and followed by two other packs at intervals of two weeks. The tumor began to recede at once and at the end of five weeks no external swelling remained.

On admission the radiograph showed a peculiar diffuse fading of the upper half of the shaft of the radius, and a faint line from the old fracture. The outline of the slightly swollen shaft was smooth (Fig. 1); there was no

bone formation, no point of perforation, or area of erosion of the shaft, all of which features told against osteogenic sarcoma. The prompt recession

FIG. 1. Diffuse endothelioma of radius. Diffuse absorption of shaft; spontaneous fracture; invasion of soft parts.

under radium was also quite unlike our experience with osteogenic sarcoma (Fig. 2). With the recession of the tumor the shaft was well restored and normal function regained. The patient left the hospital with instructions to return weekly for observation, which was continued for several months.

FIG. 2. Diffuse endothelioma of radius. After radium treatment.

The patient then came under the care of her original physician who noted persistence of the nasal and ocular symptoms, and, regarding the tumor of the radius as luetic, he instituted vigorous treatment by salvarsan. The injections, however, were followed by severe toxic symptoms, vomiting, bloody urine, collapse, and progressive anemia. Later injections of cacodylate of sodium were administered for the anemia. The patient failed steadily and the tumor of the arm began to reappear. There was now an

irregular fever up to 103° F. The urine failed to show Bence-Jones protein.

In October, 1920, the patient returned to the Memorial Hospital with a definite recurrence of the tumor, and owing to the conflict of opinion, a portion of tissue was removed for diagnosis. It proved to be a round cell growth of the above-mentioned type. Other tumors had now appeared plainly in the skull. There was exophthalmos. The eye grounds showed choked disc and nerve atrophy. The radiograph of the lungs was negative. Anemia and cachexia progressed rapidly, and death occurred on December 23, 1920. The total duration was about thirty months.

During the past four months I have seen six other cases of this disease. They occurred in subjects from fourteen to nineteen years of age. The bones affected were tibia, ulna, ischium, parietal and scapula. The tumors grew rather slowly, requiring some months to attract attention, but they were accompanied by attacks of pain and disability. One boy complained only of intermittent attacks of pain after exercise during the summer, but in November a smooth swelling appeared over the upper half of the leg. Several tumors were found to fluctuate in size, a symptom due to their vascularity. All were rather painful and tender.

The radiographs give characteristic features on which a diagnosis may be based with considerable certainty. A large portion or the whole of the shaft is involved, but the ends are generally spared, contrary to the rule with osteogenic sarcoma. The shaft is slightly widened, but the main alteration is a gradual diffuse fading of the bone structure. Bone production has been entirely absent. Some of the bones appeared honeycombed. Perforation of the shaft and sharp limitation of the process are wanting. The central excavation with widened bony capsule, as seen in benign giant cell tumors, is missing. The radiograph is therefore rather specific.

Under radium treatment the tumor recedes and the shaft gradually becomes well defined with little deformity and no eccentric bone formation.

In seven cases the tissue was examined microscopically, and in all the structure was nearly identical. The growth was composed of broad sheets of small polyhedral cells with pale cytoplasm, small hyperchromatic nuclei, well-defined cell borders, and

complete absence of intercellular material. Hydropic degeneration often affects large islands of cells, in which only nuclei and cell borders are visible. Necrosis occurred after radium applications. There is very little desmoplastic quality, but the tumor cells readily infiltrate muscle and pass along the fasciæ. In none were pulmonary or other forms of metastases observed. In the case cited the tumors of the skull were regarded as primary and of long standing. In some sections the cells were of increased size, while in others they were smaller and more compact, and approached the morphology of plasma cells. However, no definite areas of plasma cells have been seen in any case.

The probable endothelial nature of the tumor was suggested by the form of the cells, and especially by the appearance in broad

FIG 3. Diffuse endothelioma of bone. Compact structure of large polyhedral cells.

sheets of polyhedral cells without intervening stroma (Fig. 3). This origin, however, did not seem to be fully supported until I encountered sections in one case in which the cells were found to line a complex series of fine channels inclosing intact blood (Fig.

FIG. 4. Diffuse endothelioma of bone. Showing blood sinuses lined by tumor cells.

4). Here the endothelial character of the cells was quite pronounced, but they were much smaller than those occurring in angio-endothelioma, with which this tumor is doubtless closely related. In other portions of the same growth the cells appeared in diffuse sheets without capillary lumina, as seen in the other tumors of the series.

The exact point of origin of the growth is not clear, but the

early rarefaction of the bone indicates that the disease begins in the blood vessels of the bone tissue. Yet an involvement, simultaneous or early, of the vessels of the bone marrow can not be excluded. In the discussions of multiple endothelioma in the literature some authors thought they could trace the origin to the vessels, blood or lymph, of the periosteum. Many multiple endotheliomas, as in Marckwald's case, have appeared well within the bone marrow.

The designation of the tumor as endothelioma rather than as myeloma seems advisable, since myeloma is properly reserved for tumors derived from the specific cells of bone marrow.

The possible relation of the endothelial tumor to plasma cell or other forms of multiple myeloma deserves consideration, but the evidence at present available indicates that the two processes are distinct. I have found no definite plasma cells in any of the specimens. Plasma-cell myeloma is nearly always multiple and often very widespread. Bence-Jones protein has not appeared in any of the cases of endothelioma, but is often absent in myeloma. Multiple myeloma also perforates the bone rapidly and destroys it completely, while these tumors cause slow, rather diffuse rarefaction.

A relation to the angio-endotheliomas and other forms of endothelioma, solitary and multiple, described in the literature, must be assumed to exist. Most of these tumors accessible in the literature have occurred in adults and were clearly recognized as endothelioma. All the tumors of the present series have occurred in children, and with one exception they have been solitary.

The main point of the present communication lies in the demonstration that there is a rather common tumor occurring in young subjects, commonly identified with osteogenic sarcoma, and usually called round cell sarcoma, which is really of endothelial origin, and which is marked by such peculiar gross anatomical, clinical, and therapeutic features as to constitute a specific neoplastic disease of bone.

Discussion:

DR. LARKIN: Dr. Ewing's contribution was such an illuminating one that I think a discussion of the study he has made of bone tumors for many years would be hardly possible in a short time. The idea which he has tried to give us of the endothelial origin of this class of tumors which we have been wont to regard as sarcomas for many years seems to be most convincing. If you look back at some of the cases which have been reported by a number of observers, I think that Dr. Ewing's ideas meet with the more radical views which we have of the conception of tumors. I believe that when you commence to look over a great many of your tumors which for many years have been classed as sarcomas that the more recent view of classifying them according to the genesis of the type of cells from which they spring will force us to accept Dr. Ewing's idea of the origin of this particular class of tumors. Not long ago Dr. Ewing reported a number of tumors in lymph nodes of endothelial origin. It was a notable contribution to pathological science, and I think that his views as expressed to-night represent the more modern view, so that we will have to look over and classify a good many of our bone tumors belonging in the class of angioendothelioma.

DR. MOSHCOWITZ: I would like to ask whether any oxidase stains were made on the sections, and I would like to know whether any metaplastic bone formation was noticed. It seemed to me in one of the lantern slides there were distinct shadows of new bone formation. This would perhaps make us skeptical in regard to accepting the endothelial interpretation.

DR. SYMMERS: I should like to ask if there was any possibility of these individuals suffering from primary tumors of the kidney, notably the so-called hypernephromas, which often metastasize to bone, and the histology of which is not unlike that of the preparation thrown on the screen.

DR. EWING: I do not believe that any of the modern methods of determining biological differences of tumor cells were used. I do not consider them reliable differential signs and there are contributions in the recent literature which point out the uncertainty of these reactions in myeloma. Perhaps Dr. Martland will come to my help and tell you about his work on one of the cases.

In regard to metaplastic bone formation, if there were such metaplastic bone formation I think we should have to abandon our idea of an endothelial origin. That is one of the things the tumor does not show, and while this might be indicated as a possibility it certainly cannot be proven by X-ray plates, but only by microscopical study, and that study indicates the absence of such bone formation. In the gross specimen exhibited there are trabeculae of bone at some distance from their original position which I think can be explained as mechanical displacements resulting from the growth of the tumor. The microscope shows that these trabeculae are dissolving bone and not forming bone. The point which our President raises in regard to a primary tumor elsewhere has been the main question in the minds of those who are inclined to recognize endotheliomas in bone. I

think in the angio-endotheliomas which are very destructive and which contain large blood vessels filled with blood, the cells do look like the large clear cells of the papillary carcinoma of the kidney, but in this tumor we have an entirely different type of cell, which I think Dr. Symmers would recognize as different from those of any tumor of the adrenal or kidney.

Another point is that these tumors occurred in young subjects, and there were no signs of malignant tumors elsewhere. One of the patients lived for two years. Renal tumors do not occur in young subjects of this type. I won't say they never occur, but that is not the age incidence of metastasizing clear-cell carcinoma of the kidney. It occurs in adults or older people. The age incidence is not so much against the origin of the angio-endotheliomas from renal tumors; angio-endotheliomas occur in adults. I would not offer a diagnosis of angio-endothelioma of bone in an adult without great care. Diffuse endotheliomas of children are different. I do not think the same suspicions surround them of possible metastatic origin that exist with the others.

DR. MARTLAND: Dr. Ewing's last case was a boy about seventeen years of age with a tumor on the parietal bone of two months' duration. We thought he might have multiple myeloma (Kahler's disease). Sections were stained for oxidase granules and were negative. He was examined very carefully for evidence of a primary growth elsewhere, especially to rule out hypernephroma or kidney tumor, and his skeleton was X-rayed for other growths with negative results.

I think Dr. Ewing has offered a distinct contribution to the pathology, diagnosis and treatment of malignant primary disease of bone, in calling attention to this type of lesion, because it has undoubtedly been diagnosed by most pathologists as osteogenic sarcoma.

Dr. Ewing states that these tumors are possibly amenable to radium treatment. In osteogenic sarcoma, especially the periosteal variety, amputation and resection have offered little hope (Bloodgood's series showing less than 4 per cent. of cures).

The treatment of malignant bone tumors is therefore so hopeless that it seems to me before any mutilating amputation or resection is performed an absolutely accurate diagnosis should be made. Such a diagnosis can in many instances be made from the X-ray in conjunction with the situation, age of patient, etc. But most cases, I believe, will require an exploratory operation to obtain an accurate diagnosis. The exploratory operation must be done under proper technique to prevent spreading of tumor, especially myxomatous tissue (cauterization with carbolic or actual cautery). If all means fail to make a diagnosis of malignancy, the tumor should be treated as a benign one.

CHEMICAL CHANGES IN THE BLOOD IN NEPHRITIS

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As is well known, the blood acts as the common carrier of food products to the tissues, and of waste products to the organs of excretion, and further aids in maintaining the neutrality of the body tissues and the normal osmotic relations. Oxygen, for example, is carried from the lungs to the tissues by the blood, while carbon dioxide is returned to the lungs for excretion by the same medium. Likewise the food nitrogen in the form of amino acids is transported by the blood to the various tissues, while the nitrogenous waste products, such as urea, uric acid and creatinine, are carried to the kidneys for excretion. The kidneys normally eliminate the end products of nitrogenous metabolism quickly and quite completely, so that in health they are never present in the blood in high concentration, but with impairment in renal function these substances may accumulate.

Normally the neutrality of the blood is maintained in considerable part by the blood bicarbonate. In acidosis, whether it be caused by the formation of β -hydroxybutyric acid as in diabetes or the non-elimination of acid phosphate as in nephritis, these acid substances combine with the bicarbonate, robbing the body of its alkali reserve, and thus lowering the CO_2 combining power of the blood.

The maintenance of the normal osmotic relations of the blood would appear to depend in large part upon the blood chlorides. In the so-called parenchymatous nephritis the ability to excrete the chlorides is impaired. To preserve the normal osmotic relations of the body fluids water is retained and edema results.

Usually the sugar of the blood is maintained at the very constant level of about 0.1 per cent., presumably through the glycogenic function of the liver, but in conditions of defective glycogen

storage, with or without defective glucose oxidation, we have an increase in the blood sugar. When this exceeds the threshold level of about 0.15 to 0.18 per cent., the protective mechanism of the kidney allows the excess of sugar to escape into the urine. In so-called renal diabetes, however, this threshold is lowered, while in advanced diabetes, with renal complications, it is frequently raised. Nephritis is quite generally accompanied by a mild hyperglycemia.

From the foregoing it is apparent that kidney disease may result in a change in the blood content of such constituents as uric acid, urea, creatinine, CO_2 , chlorides and sugar, in addition to many others. It should be borne in mind that the clinical symptoms of nephritis are the result of the pathological condition of the kidneys only indirectly, but rather the result of the accumulation of various products in the blood and tissues due to deficient kidney function.

How may blood analyses be used practically as an aid in the diagnosis, prognosis and treatment of renal disease? The function of the kidneys is to eliminate nitrogenous and other waste products from the body; consequently, a diagnosis based on the impairment in kidney function is especially useful, since it points the way to an intelligent treatment. The routine urine tests of specific gravity, protein, casts and blood cells are of considerable value in indicating the presence or absence of renal disease, but they furnish little information regarding renal function. It is for this reason that the blood tests are particularly useful, since they enable us to gauge the severity of the condition and formulate an opinion regarding the probable outcome. For example, a case may show a moderate amount of protein in the urine with a perfectly normal blood urea, and thus have a favorable prognosis, while another case may give a trace or even a negative test for protein, but have a high blood creatinine, indicating that a fatal outcome is a matter of only a few weeks or months. In the treatment of nephritis it will be conceded, I think, that dietary restriction in nitrogen or chlorides can be made intelligently only when a knowledge of the degree of impairment in the function of eliminating the nitrogen or chlorides is at hand.

There would appear to be little doubt that cases of incipient nephritis are accompanied by an appreciable rise in the blood uric acid, although a rise in the blood urea can probably be taken as a safer sign of impaired kidney function. It is certainly true that the urea nitrogen falls within very narrow limits for perfectly normal individuals. As soon as one passes to hospital patients, however, figures above 15 mg. of urea nitrogen are found. Figures over 20 on the usual restricted diet of the hospital would suggest impaired kidney function. Creatinine appears to be more readily eliminated than either uric acid or urea, and it is not, as a rule, until the blood urea has doubled, or more than doubled the normal, that there is a very appreciable increase in this purely endogenous waste product derived apparently from muscle metabolism. The normal for the creatinine of the blood is approximately 1 to 2 mg. per 100 c.c., and figures over 3.5 mg. can be viewed with grave concern, while over 5 mg. are almost invariably indications of an early fatal termination. The only possible exceptions are cases where the retention is due to some acute renal condition, such as acute nephritis and mild bichloride poisoning.

Normally the CO_2 combining power of the blood plasma of the adult amounts to 55 to 75 c.c. per 100. In moderate acidosis figures between 30 and 40 are observed, while in severe acidosis the figures are below 30. All advanced cases of chronic nephritis suffer from acidosis, and in some cases this is apparently the cause of death. It may also be noted that cases of acute nephritis occasionally show marked acidosis.

In parenchymatous nephritis, if we may be allowed to use this term, the findings are quite different. Here the nitrogen retention is comparatively small, although the examination of the blood generally discloses a retention of chlorides. The figures for urea nitrogen seldom exceed 30 mg., except in the terminal stages of the disease, and generally fall between this figure and 15. The figures for chlorides, expressed as sodium chloride, frequently exceed 0.6 per cent. for whole blood and 0.7 per cent. for plasma.

It is of interest to note that many advanced cases of malignancy, possibly as a result of the toxemia, give the chemical blood picture of moderately severe nephritis; also that many cases of pneumonia show definite evidence of nitrogen retention; while in the terminal stages of the disease a severe acidosis quite generally develops, apparently as an indirect result of the marked arterial oxygen unsaturation of the blood.

Relatively high figures for the nitrogenous waste products are frequently noted in intestinal obstruction and lead poisoning, while a slight retention is often observed in gastric and duodenal ulcer, possibly for the same reason that retention is found in intestinal obstruction. The moderate nitrogen retention sometimes encountered in syphilis and certain cardiac conditions is apparently due to renal complications.

Since the blood findings in eclampsia are to be considered by Dr. Killian in the next paper, they will not be discussed here.

Kidney disorders, according to ordinary clinical groupings, give the following chemical blood pictures:

1. *Incipient nephritis*: Slight nitrogen retention (high uric acid, slightly elevated urea).
2. *Advanced chronic nephritis*: Marked nitrogen retention (including high creatinine), with or without severe acidosis.
3. *Acute nephritis*: (a) Mild,—moderate nitrogen retention; (b) severe,—moderate or marked nitrogen retention, with or without acidosis.
4. *Parenchymatous nephritis*: Slight or only moderate nitrogen retention, generally definite salt retention, occasionally marked hypercholesterolemia.

Although a diagnosis can best be made in connection with the full clinical history of the case, the findings of groups 2 and 4 are so typical as to allow in most instances of a diagnosis on the basis of the blood analysis alone. The terms employed above have been used solely with the idea of giving the different groups a simple name and without any anatomical significance.

A few illustrative cases which fall into the above groups are tabulated below:

| Group | Uric Acid | Urea N | Creatinine | CO ₂ Combining Power c.c. to 100 | Chlorides as NaCl Per Cent. |
|--------|--------------------------|-----------|------------|--|--------------------------------------|
| | Mg. to 100 c.c. of Blood | | | | |
| 1..... | 9.5 | 25 | 2.5 | | |
| 2..... | 7.7 | 200 | 26.7 | 12 | |
| 2..... | — | 147 | 5.7 | 40 | 0.50 |
| 3..... | — | 50 | 2.5 | 50 | |
| 3..... | 11.2 | 93 | 5.9 | 54 | |
| 3..... | 9.5 | 44 | 3.5 | 22 | |
| 4..... | 2.3 | 28 | 1.9 | 56 | 0.70 |
| 4..... | 4.5 | 22 | 2.1 | | Increased |

Normal figures for the uric acid of the blood may be given as 2 to 3 mg. per 100 c.c., urea N 12 to 15 mg., creatinine 1 to 2 mg., CO₂ combining power 55 to 75 c.c. per 100 of plasma, and chloride of whole blood 0.45 to 0.50 per cent.

SIGNIFICANT CHEMICAL CHANGES IN THE BLOOD IN THE TOXEMIAS OF PREGNANCY

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The first step in the study of the chemical changes involved in the toxemias of pregnancy was to determine whether in fairly comprehensive analyses of the blood a large group of representative toxic pregnant cases manifest any characteristic variations when compared with normal pregnant cases. The results obtained in this first step of the investigation are presented below, and, we believe, they admit of the deduction of definite conclusions.

At the outset it was evident that the toxic cases might be conveniently divided into three distinct groups:

1. Nephritic toxemias—including a group of cases that in their previous histories gave evidence of a preexisting nephritis which was not consequent to the pregnancy, but rather was aggravated by it.

2. Hepatic toxemias or true eclampsias—comprising cases that gave no evidence of preexisting impairment of renal function. By the clinical symptoms alone these cases can be readily differentiated from those of the former group.
3. Mixed toxemias—the cases within this group present evidence of a mild impairment of renal function which, however, resulted from the hepatic toxemias. The clinical findings alone are not sufficient to differentiate this group from group 2.

Four cases, carefully selected as normal pregnancies, showed low normal or slightly decreased figures for nonprotein nitrogen, with proportionately decreased urea nitrogen. The urea nitrogen formed from 45 to 50 per cent. of the nonprotein nitrogen. Uric acid, creatinine, chlorides and sugar proved to be normal, but the carbon dioxide combining power was slightly lowered. No hypertension was observed. The urine, on the other hand, from time to time contained traces of protein.

Four patients, all multiparæ, suffering from nephritic toxemias, were studied. Of these cases three showed impaired nitrogen excretion, whereas the fourth was a case of parenchymatous nephritis, with chloride retention. In the first three cases the nonprotein nitrogen was increased from 45 to 106 mg., the urea nitrogen in a similar manner was elevated from 28 to 72 mg., forming from 62 to 67 per cent. of the nonprotein nitrogen. The uric acid figures ranged from 4.8 to 8.1 mg., but the creatinine was only slightly increased. The fourth case showed no evidence of nitrogen retention, but the chloride concentration was considerably increased (0.52 per cent.) and was found to be associated with a marked edema. The decrease in the carbon dioxide combining power was not greater than in the normal cases. Large amounts of protein and occasionally casts were found in the urine. Further, these cases were characterized by a pronounced hypertension, and albuminuric retinitis with marked disturbance of visual acuity. Following the removal of the foetus from the uterus, there was at most only a slight general improvement, with

practically no return to normal in the chemical composition of the blood.

Twelve cases of hepatic toxemias or true eclampsias came under our observation, including two cases of pernicious vomiting and two cases of post-partum eclampsia. All of these cases were primiparæ save three, but the previous pregnancies of these three had also been toxic. In all instances a rise in the non-protein nitrogen (34 to 56 mg.) was found; the urea nitrogen, on the contrary, was definitely decreased, constituting from 15 to 34 per cent. of the nonprotein nitrogen. The increase in the uric acid (3.5 to 11.0 mg.) was very striking. The greatest disproportion of urea nitrogen to the nonprotein nitrogen, the highest uric acid figures and the largest output of protein in the urine were found in the most toxic cases. This observed increase in uric acid, we believe, may be attributed to a renal irritation resulting from the toxemia, producing a slight impairment of kidney function.

No disturbance of the creatinine concentration of the blood was noted, but in the majority of cases there was a mild hyperglycemia and a pronounced decrease in the carbon dioxide combining power of the blood. In fact, two cases died of post-operative acidosis. A normal chloride concentration of the blood was found to be the rule, except in a few cases where high chloride figures were encountered in edematous patients. The protein excretion varied from a trace to a large amount. Although all cases had increased blood pressures, this elevation was not as pronounced as in the nephritic toxemias. Furthermore, unlike the nephritic toxemias, the cases in this group manifested a prompt improvement as judged by the chemical composition of the blood and as well by the clinical signs, following the removal of the foetus from the uterus. Finally, no pathological changes were noted in the examination of the eye-grounds.

The mixed toxemias, apparently, represent a more severe degree of toxicity than the hepatic toxemias. The toxic factors in both groups of cases, no doubt, are identical, but in the latter it has produced a more severe impairment of renal function, result-

ing not only in the retention of uric acid, but likewise in a moderate accumulation of urea nitrogen. The nonprotein nitrogen was found to be from 56 to 64 mg., and although the urea nitrogen was considerably increased, nevertheless it formed but a small portion of the nonprotein nitrogen (32 to 38 per cent.). In this particular these cases differ from both the nephritic and hepatic toxemias; in other respects, however, they gave findings similar to the hepatic toxemias.

Dr. I. J. Levy read a paper on "The Relation of the Histopathology of the Kidney to Blood Nitrogen," which will appear in full elsewhere.

Discussion:

DR. MOSHCOWITZ: Dr. Levy's presentation interested me enormously. I wish I possessed Dr. Levy's confidence in trying to partition out the various types of nephritis as he has done. For years I have been attempting to correlate function and anatomy in disease of the kidney and have been unable to predict the "type" of nephritis that will be found at autopsy from functional tests alone. It seems to me that such a prediction will resolve itself largely into a matter of guesswork. There are various reasons for this. The most important is the fact that in the past we have been regarding the "type" of nephritis as an end product. It seems to me rather that these "types" are not pure in the biological sense, but run into each other, and that they represent stages in a fairly well-defined pathogenesis beginning in an early glomerulo-nephritis and ending in the familiar contracted kidney. I refer now, of course, only to those kidneys that may be comprised under the term arterio-capillary fibrosis. The parenchymatous, the kidneys of sub-acute bacterial endocarditis, and the amyloid do not enter into this discussion. I propose to report shortly upon six autopsies in which marked evidences of nephritis were present during life, although at post-mortem the kidneys showed barely perceptible damage. On the other hand, all pathologists are familiar with the phenomenon of finding profoundly contracted kidneys at post-mortem although during life there were no evidences of nephritis. These patients died of something else. The point I wish to make clear is that clinical and anatomical nephritis are two entirely different things and can only be correlated in a very broad sense.

I have submitted in a number of papers the thesis that arterio-capillary fibrosis is a primary vascular disease. Whether the initial change is in the glomeruli or the terminal arterioles is not a matter of great consequence, although I believe it is in the former. All the changes that occur in such a kidney can be explained genetically from the progression of such early lesions. As Dr. Levy pointed out, the vast majority of patients with "nephritis" die a cardiac and not a renal death. They die of decompensation of the cardio-vascular apparatus just as patients do who have frank valvular

disease. This is one of the reasons why it is so hard to interpret blood figures, such as Dr. Levy and Dr. Myers have presented, in terms of anatomy. Their greatest value, as Dr. Myers pointed out, is in estimating prognosis. The trouble with these figures in attempting an estimate of renal function is that they are dependent on too many extra-renal factors of which the most important are diet, water intake, the function of other viscera, the liver for instance, and myocardial insufficiency. The latter, in my opinion, is the most important factor. Non-nitrogenous retention seems to be proportional more directly to myocardial insufficiency than to any other factor. I can confirm the findings of Rowntree and Geraghty, who showed both clinically and experimentally that tests for renal function depended largely upon the amount of chronic congestion of the viscera, a condition practically always present clinically and anatomically in nephritis. It is for this reason that a method of determining the volume output of the heart would be most desirable; unfortunately our instruments of precision afford no guide for the determination of this highly important function.

DR. SCHWARZ: I should like to say a few words from the clinical standpoint, that we endeavor to get some of the types straight in our minds. I do not think we should look at this quite as darkly as Dr. Moschowitz does, for observing these cases at the bedside there are certain distinct groups which are diagnosticated by the chemical examination of the blood. In the first group we find blood in the urine without an increased blood pressure, some reduction in the amount of urine excreted and some retention of the nitrogenous substances in the blood. These cases have an etiological factor—either scarlet fever or naso-pharyngeal conditions. These may or may not clear up and become chronic. The second group without any etiological factor but sometimes, however, due to diphtheria, has edema which is more or less persistent, no increased blood pressure, no retention of nitrogenous substances in the blood but a marked increased cholesterol in the blood. The third type not seen so frequently in children, but more often in adults, is always associated with hypertension and changes in the eyeground indicative of albuminuria retinitis, marked polyuria, polydipsia and low specific gravity, and is associated with sclerotic changes in the kidney and no change in the blood chemistry.

LIPOMA OF THE UTERUS

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In view of the infrequent occurrence of lipomata of the uterus, it was thought on encountering this case that it would be of interest to report it. Including the case here reported, there

are but seventeen such tumors on record. Ellis quotes statistics of Williams, who found no case among 2,649 uterine tumors collected from four large London hospitals, and statistics of Gurlt, who encountered no case among 4,115 uterine tumors on record in the Vienna hospitals. In a review of the Index Medicus from 1890 through 1919 I found no case reported from New York City. This is the first case to occur among 14,500 operative specimens of all types examined at the Lenox Hill Hospital.

Of the seventeen cases on record, ten were collected from the literature by Seydel, who added a case of his own, in 1903. Pollack reported an additional case in 1903. Elkins and Haythorn in 1917 reported a case and enumerated the three cases reported in the interval between 1903 and 1917 by Ellis (1907), Sitzenfrey (1910), and Ley (1914).

The various case reports, with their comments, which were written from time to time as the tumors were encountered, cover quite comprehensively all that is known of the condition. This is particularly true of the paper written by Seydel, around whose paper the literature may be said to center. He reviewed critically all the literature to date, admitting to his list of cases only such as had been carefully investigated and described and definitely proven to be lipomata or lipomyomata. Knox in 1901 was the first one in recent years in this country to describe a case, though Schoinski in 1880 described a case which was accepted by Seydel.

Clinically there is nothing to distinguish these tumors from other non-malignant tumors of the uterus. It may be noted that the patients were for the most part from fifty to sixty years of age, though one patient with a cervical polypoid lipoma was but twenty-eight years old.

The tumors have varied both in their location and in the details of their structure. Four occurred as cervical polyps, the remaining thirteen as tumors of the body of the uterus. Seven, including the one here reported, are listed as simple lipomas. Of these seven tumors, two occurred as cervical polyps. The other ten tumors are classed as lipomyomas. These showed varying quantities of fibrous and smooth muscle tissue in the septa be-

tween the fat alveoli, while one tumor also showed sarcomatous areas. Of the ten lipomyomas two occurred as cervical polyps. The distinction between lipoma and lipomyoma is an arbitrary one and may vary with the viewpoint of the author. In general, it seems that the name lipoma has been applied to those tumors where the fatty tissue seemed to be sharply set off against the surrounding fibromuscular tissue and where no muscle strands entering the fatty tissue from the capsule have been evident. Those tumors, on the other hand, where the fibromuscular tissue has been seen very evidently to enter the fatty tissue from the capsule and disperse among the fat cells have been called myolipoma, or fibromyolipoma. But between the pure lipoma and the tumor, with thick strands of fibromuscular tissue entering the fat zone, there are all gradations. Thus in the tumor I shall describe the fibromuscular elements separating the alveoli of fat cells are barely to be distinguished at the periphery of the tumor. Taking the viewpoint that these fibromuscular strands are remnants of uterine tissue in the process of being pushed aside by the growing fat cells, I have classed the tumor as a simple lipoma. Perhaps it would be better to follow the lead of Elkins and Haythorn and refer to this entire group of tumors simply as "fatty tumors of the uterus."

Of the histogenesis of the fat cells occurring in these tumors nothing is known. The theories advanced are:

I. That they result from a fatty degeneration of the fibrous or muscular tissue in fibromyoma of the uterus. In support of this theory it has been urged that fatty degeneration has been observed in the muscle cells and connective tissue of these "fatty" tumors, and one author believed that he could trace the process in its various stages from beginning fatty degeneration to completed fat cell. This idea is contrary to present ideas of the specificity of tissue growth. Moreover, some of the tumors have shown no fatty degeneration whatsoever in their connective or muscular tissue.

II. That the fat cells arise by multiplication of fat cells congenitally misplaced.

III. That the fat cells arise by multiplication of fat cells brought into the uterus along with the blood vessels. Seydel quotes R. Meyer on this point, the latter stating that he has observed fatty tissue accompanying blood vessels into the uterus, though never deeply.

The case reported below occurred on the Gynecological Service of Dr. Oastler at the Lenox Hill Hospital:

The patient was a woman sixty years of age.

Family History: No significance.

Past History: No significance.

Menstrual History: Onset at thirteen years; last period fifteen years ago. No bleeding or discharge since.

Obstetrical History: One child thirty-five years ago, with normal delivery. No miscarriages.

Present Illness: The only symptom was pain in the left lower quadrant of the abdomen of four weeks' duration.

Physical Examination: General examination showed nothing of importance. Pelvic examination revealed a large tumor apparently connected with the uterus.

Working Diagnosis: Fibromyoma of the uterus.

Operation: A large tumor incorporated with the uterus was found lying in Douglas's pouch and bound to the adjacent viscera by adhesions. The entire mass was easily delivered and a supravaginal hysterectomy done.

The patient made an uneventful recovery.

Gross examination of the specimen reveals a tumor incorporated with the remnants of the uterus, and a tube and ovary. The tumor is roughly globular in shape and measures about five inches in diameter. In its growth it has distorted the uterus, so that its original position cannot be made out, but it can be seen that it has involved the body of the uterus and that it occupies an intramural position. On section the tumor has an almost uniform pale yellow color. A delicate connective tissue framework is present, but this forms a very inconspicuous part of the picture. The tumor is for the most part sharply marked off from the remnants of uterine wall which surround it, but in places strands of tissue merging with the uterine wall may be seen to enter the tumor proper and subdivide within it.

Microscopical examination shows the tumor made up for the greater part of mature fat cells arranged in bundles of various sizes and separated by strands of connective tissue showing various stages of hyaline degeneration. At the margin of the tumor it can be seen that the fat cells abut directly upon a wall showing connective and smooth muscle tissue. Both muscle and fibrous tissue may be demonstrated as components of the strands described in the gross as merging with the uterine wall and then subdividing as they enter the tumor. The thicker strands of fibromuscular tissue in the tumor and the fibromuscular tissue forming the capsule of

the tumor are seen to contain fat cells in small groups or even isolated. It thus appears that there is no sharp line of demarcation between the fatty tumor and the remnants of uterine musculature present, though to be sure the invasion of the uterine wall by the fat cells is limited to the areas immediately adjacent to the tumor. This lack of sharp demarcation between the fatty tumor and the uterine wall has been described in other cases.

To me the most plausible interpretation of the above microscopic picture is that we are dealing with a lipoma of the uterus which in its growth has pushed aside the fibromuscular tissue, and that this latter tissue has then undergone degeneration. Certainly the fibromuscular tissue present does not suggest growth activity. For these reasons I have classed the tumor as a lipoma, though realizing that such a classification is open to criticism.

In concluding, I wish to thank Dr. Rohdenburg, who called my attention to the tumor and permitted me to report it from the laboratory.

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Discussion:

DR. WOOD: Small masses of fat are not uncommon in fibromyomata, but the appearance of a large discrete tumor of this type is a very great rarity. It seems to me that the most natural thing to assume is not that the tumors are formed by a degeneration of the muscle tissue, but are independent growths, possibly with a developmental basis.

DR. LARKIN: Seydel's article on this peculiar condition of the uterus is probably one of the best monographs which has been given to us on the pathology of this very rare condition. If I remember rightly his idea was that the fat was more or less of a metaplasia of connective tissue which might mass itself in a tumor formation or might occur in discrete areas in other uterine tumors, especially fibromyoma. I do not think he was wrong in his interpretation, because those who have had an opportunity of examining many fibromyoma find microscopically some conditions which seem to tend to fat transformation.

CONCERNING A PHAGE (LYTIC AGENT) ISOLATED FROM TRANSPLANTABLE ANIMAL TUMORS

G. L. ROHDENBURG, M.D.

(From Columbia University, George Crocker Special Research Fund, F. C. Wood, Director)

Several years ago d'Hérelle announced that he had been able to isolate from the feces of those recovering from dysentery a substance which had the power of causing lysis of the etiological bacteria. Since that time there have been other publications dealing with various phases of the problem. D'Hérelle applied the term "phage" to the agent capable of causing this lysis.

Phages have been isolated from many sources by at least two technical methods. The phages which have been isolated from bacteria have been more or less specific in their lytic action. The nature of the phage is not yet fully determined. D'Hérelle is of the opinion that it is an ultramicroscopic organism, and the recent work of Salimbeni places the organism as a mycelium; Kabe-shima, however, presents evidence which suggests the possibility of its being enzyme in nature. Since d'Hérelle was first able to isolate the lytic substance only from the feces of those recovering from the infection, he suggested that the phage might have something to do with convalescence.

Transplantable malignant tumors in animals are roughly divided into two groups, those which in varying percentage recede spontaneously and those which do not. In spite of many experiments, the cause of this spontaneous recession still remains unexplained. The experiments recorded in this report were undertaken with the idea that spontaneous recession of transplantable malignant tumors might possibly be due to a tissue phage.

The technical steps of the experiments are simple. The tissue to be examined is obtained under sterile conditions and a cube varying from 0.2 to 1 cm. in diameter is placed in broth. The inoculated tube is incubated for a period of forty-eight hours at 37° C. The presence or absence of a phage may be demonstrated by one of two methods. At the end of forty-eight hours' growth, if the broth remains clear, it is plated on nutrient agar, isolated drops of the broth being added to the agar plate just before solidification occurs. In a second method about 0.3 c.c. of the broth is added to a sterile two per cent. suspension of red cells in physiological saline. The agar plate, or the blood tube, are then incubated at 37° C. for twenty-four hours. The presence of a phage is predicated upon either the lysis of the red cells in the saline tube or definite zones of digestion in the agar plate (Fig. 1). If the original broth culture shows bacterial growth after incubation, then it should be filtered through a Berkefeld filter, and the clear filtrate used as previously described.

Following this technic, examinations of all of the twelve

growing tumor strains in the laboratory were made. Each tumor strain was examined twice, and as controls, normal kidney, spleen, and fetal tissue were also examined. A phage was demonstrable in all.

FIG. 1.

FIG. 2.

FIG. 1. Pure phage isolated from transplantable animal tumor

FIG. 2. Phage with intentional bacterial contamination.

The examinations were again undertaken with six receding tumor strains, actively receding tumors being cultured in each instance. A phage was demonstrable in all of twelve attempts. The same technic was then applied to a rapidly growing carcinoma of the breast in the human, and a phage was also isolated.

The following observations have been made on the phage isolated from receding rat and mice carcinomata and sarcomata: Lytic action of the broth culture is demonstrable up to a dilution of 1:1200. The phage can be propagated. The phage passes through a Berkefeld filter, but is not dialyzable through a celluloidin sac. Phage cultures to which red cells have been added show, after seven to fourteen days, a gradual reduction of the hemoglobin to some other pigment derivative. One strain of phage has been propagated for fourteen generations. The addition of alcohol or glacial acetic acid to the broth culture produces a copious flocculent precipitate, which is again partly soluble in physiological saline solution and which still shows phage action after twenty-four hours' contact with the precipitating chemical. The addition of blood to phage cultures has thus far

uniformly resulted in a bacterial growth, the bacterium being a thin bacillus, occasionally occurring in chains, Gram-positive, and showing spores. This organism has not yet been identified; however, when it appears in a phage culture the lytic action of the broth very markedly decreases, or completely disappears. Contamination of phage culture by other bacteria, *i.e.*, staphylococcus, streptococcus, typhoid bacilli, *B. subtilis* and *proteus* does not inhibit or destroy the phage action.

A single injection of nonbacterial contaminated phage broth into animals bearing transplanted tumors which do not spontaneously recede does not cause recession, possibly because the blood present in the body brings about the development of the bacterial growth previously referred to. If any action be demonstrable, it is a stimulation of growth, though this can not be asserted positively. Animals bearing tumors which do not spontaneously recede when injected with the bacterial growth show no decrease in growth energy.

Discussion:

DR. NOGUCHI: I would like to ask if you determined the optimum hydrogen ion concentration in which the phage acts.

DR. MACNEAL: I should like to know just what the action is on the agar. I take it these are agar plates to which a drop of this broth has been added. Apparently there is a hollowing out of the agar, and in some instances there seems to be a bubble of air in it. Of course these are formalin preparations, and it is difficult to tell what the original appearance may have been, or what is the interpretation of the change in the agar when it was fresh. Is it liquefaction, digestion of the agar, or what?

DR. WOOD: I would like to ask Dr. Rohdenburg to continue his argument a little further against or for a ferment. As far as my own opinions go, I watched the work with a great deal of interest, and I have not the slightest idea what the explanation is. I think we will have to suspend all judgment until more data have been collected. The phage evidently has nothing to do with the disappearance of tumors, because it is found in progressively growing tumors, and also in human tumors in which there is no possibility of regression.

DR. ROHDENBURG: These experiments are really only at their beginning, and no work has been done on the hydrogen ion concentration. I would add that the phage can be demonstrated by using 200 c.c. of salt solution to which 15 or 20 c.c. of ordinary nutrient broth and a fragment of tumor have been added.

The original appearance of the plates, when fresh, was perfectly smooth, and in those experiments where precipitation was obtained with acetic acid and alcohol, we could see, because of the precipitate, where the drop was placed. After twenty-four hours the surface of the agar was eroded. There was no liquefaction that was demonstrable, though the water of condensation on the plates might be due to the evaporation of the liquefied agar.

DR. MACNEAL: Did you drop the broth on before the agar was solidified?

DR. RÖHDENBURG: Just before it was solidified.

THE SIMULTANEOUS OCCURRENCE OF A METASTASIZING HEPATOMA AND AN EPITHELIOMA OF THE ESOPHAGUS

DE WITT STETTEN, M.D.

Since the careful analysis by Harbitz¹ considerable interest has been shown by oncologists in the question of the simultaneous occurrence of multiple tumors—particularly of different neoplasms in diverse organs. It has recently been my fortune to have observed a rather unusual case of this nature, and it was with some trepidation—as I am only a surgeon—that I accepted your secretary's invitation to present this case before your Society.

The patient was a man, fifty-nine years of age. For about a year he had had vague abdominal symptoms, with loss of weight. Shortly before I saw him in October, 1920, he had had several attacks of pain, which resembled biliary colic. On examination, he was decidedly emaciated and a moderately enlarged, slightly nodular liver could be palpated. The gall bladder region was sensitive. There was no jaundice, nor temperature. The blood showed a moderate secondary anemia. The Wassermann test was negative. Radiography showed indirect evidence of gall bladder disease.

The probable diagnosis of carcinoma of the liver was made, but in view of the gall bladder symptoms, and the possibility of an error in diagnosis, an exploratory laparotomy was advised and performed on October 14, 1920. The liver was found diffusely enlarged, the surface was somewhat nodular and irregular in consistency, but it was difficult to find distinct nodes. The liver surface did not suggest a typical carcinoma. One small, definite nodule, lighter in color than the rest of the liver surface, and situated near the liver edge, to the left of the suspensory ligament, was excised for

diagnosis. The gall bladder was found to contain numerous calculi and a cholecystectomy was done. The quadrate lobe felt particularly hard. There was no evidence of a primary growth in the stomach, gall bladder or intestines. There were fine adhesions between the upper surface of the liver and diaphragm.

FIG. 1.

FIG. 2.

FIG. 1. Hepatoma, separated from normal liver by zone of round-cell infiltration. Low power.

FIG. 2. Hepatoma. High power.

Microscopic examination of the excised nodule showed it to be a typical Rokitsansky liver-cell adenoma or so-called hepatoma (Figs. 1 and 2). The cells, though they resemble liver cells are much larger, take a deeper stain, and are not arranged in the same orderly fashion. They possess a large amount of granular, acidophilic protoplasm and small vesicular nuclei, which generally show a single nucleolus. There is some variation in the size of the cells and nuclei and large cells with a single, large, or several small nuclei are occasionally observed. Mitosis is not active. In the center of the tumor nodule there is some fatty degeneration of the cells. The tumor is split into larger and smaller, irregular lobules by bands of fibrous tissue, but there is no tendency to form acini, the cords and islands of tumor cells being supported merely by thin-walled capillaries. The growth is partially surrounded by a fibrous capsule, though in one area tumor cells have broken through the capsule and are irregularly distributed among the surrounding atrophic liver cells, and in other places the tumor tissue is separated from the adjacent liver tissue by a zone of round-cell infiltration.

Histologically the tumor seemed to be benign. A Wassermann taken after operation showed 4 plus with natural amboceptor and negative after anti-sheep amboceptor had been added. This suggested the possibility of a syphilitic infection and it was hoped that perhaps the liver condition might be explained on that basis. Sternberg³ has called attention to the fact that in

FIG. 3. Radiograph of esophagus, showing obstruction in lower third.

certain forms of nodular adenomatous hyperplasia of the liver, compensatory to various destructive processes, great difficulty occurs in differentiating these lesions from the true adenomata. On this theory and in the hope of arresting further liver destruction, a course of anti-syphilitic treatment was begun, but soon abandoned, as it was not well tolerated and showed no results, and as a subsequent Wassermann was negative.

FIG. 4.

FIG. 5.

FIG. 4. Gross appearance of hepatomata of liver.

FIG. 5. Gross appearance of hepatomata of liver, with large necrotic tumor in center of organ.

About two weeks after operation the patient began to complain of dysphagia. X-ray examination of the esophagus (Fig 3) and esophagoscopy showed a marked obstruction, undoubtedly organic in character, in the lower third of the esophagus. Whether the lesion was intra- or extra-esophageal could not be positively established, but on November 27, 1920, a gastrostomy was performed. On December 16, 1920, the patient died from asthenia.

Postmortem examination showed the following important changes:

The liver is somewhat enlarged but very much distorted by numerous nodules which project from beneath the capsule (Fig. 4). These nodules are circumscribed, of pinkish-white color, and granular surface. They vary in size from 0.5 to 12 cm. in diameter. About the center of the organ is a large tumor of this type which has undergone complete necrosis, the necrotic material being bile green (Fig. 5). Vascular emboli are demonstrable in the gross, projecting from veins which are visible on the inner wall of the cyst left by the necrosis of the tumor tissue.

Scattered throughout the lungs are pinkish-white, circumscribed nodules ranging in size from a pin-head to 2 cm. in diameter.

FIG. 6.

FIG. 6. Gross appearance of squamous-cell epithelioma of esophagus.

FIG. 7.

FIG. 7. Metastases in lung from hepatoma.

The esophagus shows, approximately 16 cm. from the cardia, a stenosing ulcer, involving over three-quarters of the circumference of the tube and measuring 3×2.5 cm. in its greatest diameters (Fig. 6). The base of this ulcer is friable, granular, and its edges are not indurated.

FIG. 8.

FIG. 8. Squamous-cell epithelioma of esophagus. Low power.

FIG. 9.

FIG. 9. Squamous-cell epithelioma of esophagus, showing pearl formation
High power.

The microscopic examination of the tumors of the liver (Figs. 1 and 2) and of the nodules in the lung (Fig. 7) shows them to be of the same character as the nodule originally excised for diagnosis at the first operation—namely, liver-cell adenoma or hepatoma, primary in the liver and metastatic in the lung. In the liver tumors blood vessel emboli are demonstrable and there is extensive degeneration and necrosis in many of the neoplastic areas. Elsewhere the liver shows a mild degree of cirrhosis of the intralobular type.

The ulceration in the esophagus shows a necrotic surface beneath which are islands and columns of epithelial cells of the stratified, squamous variety in which intercellular bridges and occasional pearl formation are demonstrable (Figs. 8 and 9). These neoplastic cells have invaded the muscle to a considerable depth. The lesion has all the characteristics of a typical squamous-cell epithelioma of the esophagus.

In conclusion, I wish to acknowledge my indebtedness to Drs. G. L. Rohdenburg and F. D. Bullock for their help in the pathological study.

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2. STERNBERG: Aschoff's Pathologische Anatomie, 1913, Ed. 3, II, 894 and 901.

Discussion:

DR. ROHDENBURG: A number of years ago I presented a series of tumors primary in the liver, some of the gall bladder, and others of the liver cell type, and I was particularly anxious to have Dr. Stetten present this case here to-night, because at that time Dr. Ewing said one of my cases was unique in that there were metastases in the lymph nodes, and that he had never seen metastasis in a carcinoma of the liver of the hepatoma type. This particular case emphasizes that metastases do occur much more beautifully than the cases I showed.

DR. SYMMERS: Was there evidence of bile staining?

DR. STETTEN: The necrotic central tumor was bile stained.

DR. WOOD: This is an extraordinarily interesting case because it illustrates very well the question of malignancy of tumors of this type. The primary growth in the liver does not differ from the adenomata seen in cases of cirrhosis, and the carcinoma in the lung is also very close to the type we find similarly associated. The tumor shows how little morphology has to do in the determination of the malignancy of some of these adenomatous neoplasms. This is well known in connection with the thyroid tumors which may metastasize and form nodules of tissue very closely resembling normal thyroid. It is impossible to believe that without metastases such tumors are malignant. There was a little bile in some of the metastases in the lung. This is very interesting more from the general point of view of

the nature and the biological qualities of the cells. Here is a liver tumor which is malignant because it has metastasized, but the cells of which are so slightly altered from the normal liver cells that they are still able to perform a considerable function, and it is difficult to consider that their chemistry and their general biological nature are very different from the normal liver cell. I think we are all coming to the realization that the cells of a carcinoma and the cells of the original tissue from which the tumor is derived are only slightly different. At the Crocker Laboratory we are doing experiments all the time to attempt to find out some differential point between the carcinoma cell and its homologous tissue, and the more we work the less difference we find. A long series of experiments have been carried out on the question of the hydrogen ion reaction of tumor cells and the homologous tissues, and we do not find any differences. It is well known that there are no general serum reactions following the growth of a tumor. The old belief of the production of cachexia by a tumor toxin is now practically abandoned. We see animals carrying tumors corresponding to one or two feet in diameter in the human being. Such animals are not in the slightest degree cachectic, and show no evidence of ill health except that they have a large lump. Pathologists are being forced gradually to the conclusion that the difference between the carcinoma cells and the homologous normal cell of the same growth rate is most minute and escapes all analysis.

DR. LARKIN: I think the simultaneous occurrence of different types of tumor in the same individual is not at all uncommon. The occurrence of simultaneous tumors of different types was pointed out by Virchow, and it has been my privilege to study a number of such tumors. From the description which Dr. Stetten gives, especially as regards the liver tumor, it would seem to me that that tumor is unusual, and is really a hepatoma.

The simultaneous occurrence of the epithelioma of the esophagus is rather unusual, and it is worthy of great attention. It may be interesting to know that only this afternoon we had an individual brought to the hospital with a very large tumor and there was a section made from the liver on which a diagnosis of primary carcinoma of the liver was made, probably an adenocarcinoma of the gall bladder ducts. There was nothing found in the abdominal cavity except this very large tumor. The stomach seemed to be normal.

DR. STETTEN: I want to say a word about the question of cirrhosis. I was much more interested in this case from the surgical and therapeutic standpoint than from the pathological, and when we first excised the nodule and the report was received, I tried to persuade Dr. Rohdenburg that maybe we were dealing with one of those adenomatous nodules found in the hyperplasias, compensatory to destruction of the liver, and I even gave him some references to an article by Sternberg in Aschoff's Pathology, in which he distinctly says it is often impossible to differentiate these lesions from true adenomata. Dr. Rohdenburg was willing to admit that perhaps this was so. When we obtained the 4 plus Wassermann with the natural amboceptor we gladly accepted syphilis as the cause of the trouble, and hoped that we

were going to cure the man by giving him anti-specific treatment. After the first operation he actually improved somewhat and appeared to be getting better. I was interested in presenting the case, not so much on account of the nature of the liver tumor, but because of the simultaneous occurrence of the two different types of malignant tumor, suggesting that the patient exhibited a distinct tumor diathesis, upon which Virchow laid so much stress years ago.

DEMONSTRATION OF LEPTOSPIRA ICTEROIDES, WITH NOTES ON THE RESULTS OF PROPHY- LAXIS AND SERUM TREATMENT OF YELLOW FEVER

HIDEYO NOGUCHI, M.D.

(From the Laboratories of the Rockefeller Institute for Medical Research)

Leptospira icteroides was first isolated in 1918 from cases of yellow fever in Guayaquil by the speaker; later the organism was obtained from yellow-fever cases in Mérida, Yucatan (Noguchi and Kligler, 1919) and in northern Peru (Noguchi and Kligler, 1920). The finding was also confirmed in Mexico by Dr. Perez Grovas, in Vera Cruz in 1920, and by Le Blanc of the Rockefeller Institute in the same city in 1921. Gastiaburú, of the Instituto de Higiene of Lima, transmitted yellow fever to guinea pigs from cases occurring during an epidemic in Piura, Peru, in 1919.

The killed cultures of *Leptospira icteroides* were first used for protective inoculation against yellow fever in Guayaquil in 1918, where 427 vaccinations were carried out. The results were so encouraging (the morbidity rate among vaccinated and unvaccinated during the same period being 11 and 110 per thousand respectively) that a vaccine several hundred times stronger has been made in large quantities and employed in Mexico and various Central and South American countries, the total number of non-immune persons reported vaccinated being about eight thousand. The development of protection, as in the case of all vaccines of this kind, requires about ten days for completion, and persons exposed to yellow fever just before vaccination or immediately afterwards are not protected by vaccination. Exclud-

ing such instances, however, there has been no case of yellow fever among the eight thousand vaccinated in the various localities, while among unvaccinated persons during the same period and in the same areas there have been about seven hundred cases of the disease.

The use of vaccine furnishes a rapid method of elimination of non-immune persons from areas where yellow fever is epidemic. By the application of sanitary measures to eliminate the mosquito carrier and vaccination in the meantime to cut off the supply of non-immune material from the infected mosquitos, a threatening epidemic of yellow fever in Guatemala and Salvador in 1920 is reported to have been checked within one month from the appearance of the first cases, that is, before a second set of

Leptospira icteroides in the liver of the guinea pig. Guayaquil strain.
× 1,000.

cases had developed. The value of vaccination as an emergency measure does not, however, minimize the importance of the anti-mosquito operations, since both factors—the non-immune human being and the infected mosquito—must be eliminated in order to eradicate yellow fever.

A therapeutic serum is also available for treatment of yellow fever. It has already been employed in 170 cases, and persons treated before the third day of illness have almost invariably recovered, the exceptions being those cases in which the quantity of serum used was too small to have any effect. By the fourth day of illness the injuries to organs are so great as to be irreparable in severe cases of yellow fever. The usual mortality in yellow fever, fifty to sixty per cent., has been reduced to 13.6 per cent. by the use of the serum.

The records of vaccination and serum treatment presented here comprise the work of a number of observers. The initial vaccination experiments in Ecuador were carried out with the cooperation of Dr. Pareja and the Direccion de Sanidad of Guayaquil; the statistics from Central America cover the work of Drs. Lyster, Bailey, and Vaughn; for the records of Mexican cases I am indebted to the Consejo Superior de Salubridad (Drs. Vasconcelos and Casasús), to the Junta de la Sanidad de Yucatan (Dr. Hernandez), and to Dr. Le Blanc; the Tuxpan statistics were furnished by Drs. Lynn and Guadarrama; the work in Peru was done with the cooperation and assistance of Dr. Kligler and Peruvian health authorities.

A COMPLEMENT FIXATION TEST OF VALUE IN THE CLINICAL DIAGNOSIS OF TOXIC THYROID- STATES

WILLIAM N. BERKELEY, M.D.

A scientifically exact method for the clinical diagnosis of plus, minus, and toxic thyroid states would be a great boon to clinical medicine; and the problem is not insoluble, but the solutions heretofore suggested are not entirely satisfactory.

E. C. Kendall,¹ among others, has proposed the basal metabolism as a guide to the existence of hypo- and hyper-thyroid conditions. But apart from the expense and complicated pro-

cedure of this method is the objection that no one yet knows how many other clinical conditions may temporarily influence the basal metabolism in both plus and minus directions. The advocates of this method, as it makes no provision for thyroid toxins, dispose of the matter by denying the existence of such bodies.

E. Goetsch² has suggested the severity of the patient's reaction to a measured hypodermic dose of adrenalin as a measure of his thyroid activity. I can not learn that this test has proved generally confirmatory of evident clinical signs. One medical friend of mine with large clinical experience thinks it a dangerous method, causing sometimes a violent and alarming reaction. M. S. Woodbury,³ in a study of some fifty recent cases of thyroid disease at Clifton Springs, N. Y., concludes that the adrenalin test is an indicator of "general sympathetic hypersensitiveness" which may or may not be of thyroid origin. Further reports^{5, 6, 7}, from other observers are unfavorable.

It was my idea at one time that if the thyroid secretion appears in the blood in a protein form (it seems generally agreed that it is in protein form in the thyroid gland), it might be picked up by a complement fixation test and titrated. In order to try out this supposition the following experiment was repeated a number of times: A healthy young sheep was immunized by successive injections of a saline suspension of thyroids from freshly killed dogs. Using the injection as antigen, a pronounced and abundant antibody could be demonstrated in the sheep serum in the course of a few injections. But not the slightest binding could ever be observed with normal dog serum as antigen. This seems to prove either that the thyroid secretion is not present in the serum at all in protein form, or that, if so, it is in too minute amount to be available for a fixation test. As I have not found any mention in the literature of such an experiment as this, it seems worth while to record it even in its present fragmentary form.

Failing in this attempt, my attention was turned to the possibility that when the chemistry of the thyroid gland is materially disturbed, as in exophthalmic goiter, the thyroid toxins (assum-

ing for the time that such bodies exist) might be accessible to study by the same (complement fixation) method.

There is almost no literature on this subject that I have been able to find, except some pioneer work done almost ten years ago by Prof. Marinesco, and his associate, A. Papazolu.⁴ The latter of these observers claims to have found antibodies a number of times in the serum of patients suffering from Basedow's disease. He used as antigen aqueous, alcoholic, and ethereal extracts of Basedow goiters, parenchymatous goiters, and normal thyroids. Of his 38 tests 14 showed complete fixation, 12 almost complete fixation, and 12 were negative.

This work, while interesting and suggestive, dates back to the very early days of scientific serology, and seems not to have been very carefully controlled. Moreover, Papazolu used alcoholic and ethereal as well as aqueous extracts of his thyroid antigens, thereby, of course, getting fixation with many luetic subjects.

Using non-lipoidal antigens (for method of preparation and serological technique, see Mr. Koopman's note) derived from various thyroid tumors (about ten in all), it has been impossible to get fixation with the serum of Graves' disease except in the case of a single goiter kindly given us by Dr. John Rogers. This growth Dr. Rogers thought to be a true Graves' tumor. Unfortunately it was all extracted, nothing being left for microscopic examination. Antigens from four normal human thyroids gotten at autopsy under favorable conditions entirely failed to bind.

About this time, through a fortunate combination of circumstances, Mr. Koopman observed that with *normal dog thyroid* random samples of Basedow serum would bind powerfully, and that they would not bind with any other dog organ.

Starting out with this test as a guide—*i.e.*, using dog thyroid as antigen—fixation experiments have been done on more than 195 human serums, of which 44 were under suspicion of positive thyroid dyscrasia.

Of the 44, 18 were clinically undoubted Graves' disease, 2 were probably so, 14 were doubtful, and 10 were probably *not*

Graves'. I have full notes of most of these cases; in all the instances where the blood only was sent (through the courtesy of medical friends kindly interested in the research) the diagnosis was made by a colleague in whom I had unusual confidence. I believe the chances of error in this regard are reasonably remote.

The 18 Graves' cases were all one plus to four plus. The probable cases were positive; 10 of the 14 doubtful cases were positive; the ten "probably not" were all negative.

As to the controls, numbering over 140 patients, all were negative except one. This exception was a young married woman of about thirty years, with a tertiary specific skin lesion on one knee. She was not particularly nervous; her pulse was 96; her eyes and thyroid did not strike one as pathologically prominent. She had a positive Wassermann and a positive thyroid fixation. She was lost before it was possible to make any further investigation of her history and condition. All the other controls—representing nearly all the chronic and many of the common acute diseases (non-infectious)—were, as already noted, negative. About 20 were old fibrocystic goiters. About 20 more were puberty enlargements. Serum kindly sent us by Dr. George Draper from a borderland case was, he reported, negative to the Goetsch test; we found it two plus positive to the dog thyroid test. Another serum (Dr. Jos. H. Fobes) was positive to the Goetsch test, and also two plus with dog thyroid.

The new test has been repeated hundreds of times and has been checked up with all needful controls. If anyone alleges that the binding is due merely to the chance appearance in human serum now and then of a native amboceptor, then he must also explain why in more than ninety-five per cent. of the cases the native amboceptor appeared in patients with a positive thyroid dyscrasia.

Speaking further for the value of the test is the fact that in several of the positive cases which have improved very much or apparently gotten well in the last eighteen months, the test has varied concomitantly with the clinical improvement, falling from four plus to two plus, and later disappearing entirely. Dr. H. H.

Janeway, of the N. Y. Memorial Hospital, who has recently experimented extensively with radium in these cases, tells me that he considers the test of distinct value in the quantitative adjustment of such treatment to the clinical condition of the patient.

The number of cases so far observed is too small to make the suggestion more than tentative, but with this reservation I venture to hope that the new test may be found of value in several directions:

1. In the clinical diagnosis of a great many cases which are now very perplexing—early cases, late cases, borderland cases, anomalous cardiac neuroses, and thyroid tumors without definite signs of thyroid poisoning, such as unusual menstrual swellings, post-puberty enlargements, and fibrocystic goiters in the early stages. Such a test would help to differentiate exophthalmos due to other causes than Graves' disease, and would eliminate many cases of severe tobacco poisoning due to cigarettes, where the symptoms and signs (as recently noted in army soldiers and recruits) have been such as to deceive the very elect.

2. The test would aid in the adjustment of therapeutic measures to the immediate condition of the patient.

3. The test is simple, inexpensive, and absolutely harmless.

4. And finally it might throw considerable light upon the etiology of cellular tumors in general.

Subject to later modification the view may be suggested that spontaneous recovery in exophthalmic goiter is due directly to the formation of these corrective antibodies in the patient's own system; and that rest, careful feeding, and relief from anxiety contribute to the cure merely by aiding the patient's normal immunity-mechanism.

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TECHNIQUE OF COMPLEMENT FIXATION REACTION IN BASEDOW'S DISEASE

JOHN KOOPMAN

The blood of some patients who show symptoms of Basedow's disease binds complement in the presence of an antigen made from normal thyroid glands.

The reaction may be due to a specific thyroid substance which combines with an antibody in the blood of the patient.

The best method of preparing the antigen which we have been able to find is as follows: The glands are obtained under aseptic precautions as soon as possible after the dogs have been killed. Each gland is trimmed carefully and minced finely with sterile scissors. The whole mass is then ground in a mortar with a measured quantity of washed and sterilized sand and of dry sodium chloride. The amount of sand is of no importance, but the salt should be added in the proportion of 1/10 gram to each gram of gland used; a few drops of 2 per cent. aqueous solution of tricresol are added for each ten grams of thyroid. This mixture is bottled and laid away in the ice-box. For use it is made up with distilled water, using 10 c.c. of water to one gram of the original amount of gland. The sand and solid matter are removed with the aid of a centrifuge.

It is best to use the mixed glands of five or six dogs. As at present prepared, the extract contains much extraneous matter which takes no part in the reaction; if some method of securing the antigenic substance free from all foreign matter could be devised, the specificity would be enhanced. As far as we have gone, we know that the antigen slowly deteriorates even when kept under the best conditions, and after about three weeks it is necessary to obtain a new supply. Drying instantly spoils its antigenic properties and it does not withstand heating to 50° C. for fifteen minutes.

The test is set up in the form of a titration, using a constant

amount of serum which is not more than one quarter of the least amount which is anticomplementary. The antigen is used in varied amounts, beginning with an excess and ending with the least amount which can be expected to give fixation. The exact amounts used will depend upon the total volume of the test the worker is accustomed to using. At the same time an antigen control is made with the same quantities of antigen as are put in the test. This procedure will obviate the necessity of putting in a separate titration of the antigen before the test itself is made. The result is indicated by the difference between the quantity of antigen which is anticomplementary of itself and the quantity which binds complement in the presence of serum. A negative serum with the antigen will often bind less complement than the antigen alone.

A serum is considered positive when it binds complement in the presence of one half or less than one half of the anticomplementary dose of antigen, and the smaller the amount of antigen necessary for complete fixation the stronger is the reaction. Fixation is carried out for from four to six hours in the ice-box. At the present time the range is short, but with improved methods of preparing the antigen it is hoped the range will become greater.

Besides the tests on human glands and human tumors (*i.e.*, thyroid tumors), as above mentioned, we have tried the glands of some other animals, namely, guinea pig, bullock and pig, and we find that guinea-pig glands give results comparable with the dog antigen.

Much more work also remains to be done on fixation results with extracts of true exophthalmic goiters. These are now very hard to get in New York operating rooms, as surgical removal of them has gone out of fashion; and we have not been able to devise any way of keeping them in fit condition for antigen formation for more than two or three weeks.

Discussion:

DR. NOGUCHI: Was the fixation complete?

MR. KOOPMAN: Yes.

DR. NOGUCHI: How much serum was used?

MR. KOOPMAN: Not more than about one-fifth or one-sixth of the anti-complementary amount.

DR. NOGUCHI: In absolute quantities, what would that be?

MR. KOOPMAN: Using 0.10 c.c. of 10 per cent. complement that would be about 5/1000 c.c.

DR. NOGUCHI: Do you find many human serums anticomplementary?

MR. KOOPMAN: With ordinary cases perhaps one or two per cent. of the sera will be anticomplementary; and of fresh sera not more than one-tenth of one per cent.

PROBABLE SYPHILITIC INTERSTITIAL PNEUMONIA IN AN ADULT

ROLFE FLOYD, M.D.

Syphilis of the lung took a definite place in medical literature about one hundred years ago, and from that day to this it has always been a difficult and often an uncertain diagnosis for the pathologist. Clinicians, on the other hand, have not hesitated from time to time to make the diagnosis easily and often, especially about 1880, when syphilitic phthisis was a frequent complaint, curable at certain European Spas, and again very recently, when X-ray lung shadows which diminish after antisiphilitic treatment, particularly if associated with a positive Wassermann, are considered, with altogether unwarranted assurance, to be a sufficient basis for the diagnosis. Rössle, a present German writer, considers syphilis of the lung as frequent as syphilis of the liver, and Carrera,¹ working in Warthin's laboratory, considers its incidence similar to that of syphilis in the other internal organs. The average incidence, however, reported by competent pathologists of wide experience is about one or two cases per thousand autopsies.

The discovery of the *spirochæta pallida* has failed to throw the expected light on pulmonary syphilis, because it has proved practically impossible to demonstrate this organism in the lungs of adults; Koch and Schmorl² and Warthin being the only ones to find it so far.

It is thus a peculiar fact that a generation after the discovery

of the tubercle bacillus, and half a generation since the discovery of the causative agent of syphilis, the diagnosis of syphilis of the lung still rests primarily on pathological anatomy.

Gummata of the lung, both in infants and adults, are accepted as definitely luetic, though sometimes difficult to distinguish from tubercular lesions. Again the so-called white pneumonia of infants is considered syphilitic by practically all observers.

It is concerning interstitial pneumonias of adults that it is the hardest to say whether they are syphilitic or not, for this condition results from many causes besides lues; thus persistent broncho-pneumonia, lobar pneumonia followed by fibrous organization, certain forms of pulmonary tuberculosis, invasion of the lung by inflammatory connective tissue from the pleura, the peribronchitic indurations that occur with prolonged irritation by dust, some extreme types of chronic congestion and unusual changes produced by foreign substances, as in broncho-esophageal fistula, may all result in extensive interstitial changes in the lung parenchyma.

Accumulating experience, however, has gradually established the following as the characters on which an adult interstitial pneumonia is to be judged syphilitic:

1. The presence of tertiary syphilitic lesions in other organs. This is a most important criterion, as well as one of the first to be recognized. In the absence of such a lesion extreme conservatism must be exercised in considering an adult interstitial pneumonia syphilitic.

2. Gross characters of syphilitic interstitial pneumonia, which are: (*a*) location in the lower lobes; (*b*) white fibrous foci, often multiple and more or less confluent with large and small radiating fibrous bands which may reach the pleura and cause a coarse puckering of it through contraction; or similar bands arising as direct extensions of the inflammatory connective tissue wall of ulcerated and stenosed stem bronchi; (*c*) the absence of necrosis and of calcification.

3. Microscopic characters, which are more diagnostic than the gross and consist of: (*a*) an extensive inflammatory over-

growth of the pulmonary connective tissue framework, the new tissue at first full of fibroblasts and thin-walled blood vessels, later becoming more densely fibrous; (*b*) round cells scattered through this tissue especially in foci and most typical when in perivascular concentrations. The alveoli, as in interstitial pneumonia of other types, are often reduced to small spaces lined by cuboidal epithelium. Sclerosis of the arteries is frequent. Giant cells are much less frequent than in tuberculosis, while miliary gummata and necrosis are not described in this form. Masses of smooth muscle mixed in with the new areolar connective tissue have been noted by Tanaka.³ The amount of anthracosis and of elastic fiber destruction are still matters of dispute.

A complete bibliography and an extensive review of the literature is given by Carrera,¹ to whose paper the reader wishing such information is referred.

It is evident that no diagnosis can be considered beyond question on such relative grounds, and that its probability will depend on the number and importance of these features present in each particular case. It is with full realization of this uncertainty that the following case is submitted for consideration.

A woman thirty-four years old was brought into Bellevue Hospital with a general septic peritonitis of which she died three days later. Signs of consolidation and pleurisy were found over the right lower lobe, and it was supposed she had a lobar pneumonia (especially as an exploratory puncture yielded no fluid). There was an artificial anus in the left iliac fossa which she said had been made at the New York Hospital three years previously to relieve an acute obstruction. She had been told at that time that she had a tumor of the rectum, and examination at Bellevue revealed a tight stenosis.

A hæmolyzing streptococcus was found in the blood during life and also cultivated from the spleen after death.

There is no mention of a Wassermann reaction.

The autopsy, done seven hours after death, showed principally: general septic peritonitis and septicæmia; interstitial pneumonia of the right lower lobe with acute fibrinous pleurisy over it; syphilitic stenosis of the rectum, and a large fatty liver.

The right lower lobe contained but little air; it was congested and contained numerous white fibrous foci, more or less confluent in places, from 0.5 to 1 cm. in diameter, from which white strands radiated, some of them reaching the pleural surface. These zones were most numerous below and behind (Fig. 1). There was no fibrosis near the root nor any

lesion of the trachea and large bronchi except recent congestion. The overlying pleura showed an exudate of recent fibrin but was not puckered, or thickened or adherent.

FIG. 1. A small piece of the right lower lobe showing the white, fibrous zones. Natural size.

There was an annular ulcer of the rectum, starting at the anus, extending three inches upwards, and limited by a worm-eaten edge above. Massive thickening of the rectal wall beneath the ulcer caused stenosis almost to the point of occlusion.

Under the microscope the white zones in the lung consist of fibrillated and areolar connective tissue with many elongated nuclei and also many of dumb-bell and other irregular forms. The tissue is well supplied with thin-walled blood vessels (Fig. 2).

Round cells occur all through it, often in distinct foci which frequently show the remnants of a compressed bronchiole or alveolus in the center (Fig. 3). Perivascular round-cell concentrations also occur, but they are not as large or distinct as those found independent of vessels.

Pus cells lie scattered through the connective tissue, probably incidental to the general sepsis.

Compressed alveoli, oval or slit-shaped and lined by cuboidal epithelium, are fairly numerous; if a lumen persists it often contains pus cells (Fig. 3).

Bronchial remnants with higher epithelium huddled together so as to obliterate the lumen also occur; remnants of smooth muscle may be seen about them.

Arteries do not penetrate far into the new tissue. Those on the periphery often are surrounded by round cells, as already described. They show little or no sclerosis.

The lung tissue between the new connective tissue zones is airless, collapsed and congested, the collapse due either to pressure by the expanding connective tissue or to atelectasis resulting from occlusion of bronchioles.

Van Gieson's stain brings out the interstitial connective tissue zones clearly and their rather abrupt transition to areas of collapsed lung.

FIG. 2. Fibrillated vascular connective tissue from one of the fibrous zones.

Sections stained by Warthin and Starry's recent improved method showed no spirochaetes.

The rectal wall shows, in its deeper layers, sclerosis of the larger vessels and an infiltration of round cells in the perivascular spaces of both large and small vessels. The muscle bundles are separated by fibrous

FIG. 3. A round-cell focus in the new fibrous tissue, centering about a compressed alveolus lined with low cuboidal epithelium. Other similar alveoli may be seen beyond the margins of the round-cell focus.

strands which are also densely infiltrated with round cells. The more superficial layers are enormously thickened and changed into firm fibrillated tissue, very densely infiltrated with round cells, continuous with a surface layer of granulation tissue, entirely devoid of all traces of mucosa.

The liver shows a decided amount of fat in the hepatic cells and a distinct infiltration of round cells along the portal canals with a tendency to form foci. There are also pus cells along the portal canals and through the sinusoids.

The reasons for thinking this interstitial pneumonia syphilitic are: (1) the presence of typical syphilitic stenosis of the rectum and probable syphilis of the liver in the same body; (2) the situation of the interstitial pneumonia in the lower lobe, the presence of multiple white foci with radiating bands, without necrosis or calcification; (3) the enormous growth of vascular interstitial connective tissue containing many round cells in foci and perivascular concentrations.

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Discussion:

DR. MOSHCOWITZ: Dr. Floyd's remarks have offered me considerable consolation. I have a specimen in my possession which I believe is syphilis of the lung, but I hesitated to present it here because I never could demonstrate the spirochete. This lung was found in a patient in whom syphilitic lesions were found elsewhere in the body. She had a syphilitic pancreatitis and a syphilitic perihepatitis. The lower lobe of the lung was completely solid with interstitial pneumonia. I am also fully in accord with what Dr. Floyd said about the clinical diagnosis of syphilis of the lung. That diagnosis is very frequently made. If a patient has clinical symptoms of a pulmonary lesion, and a positive Wassermann is found and an X-ray shadow is present which disappears after salvarsan treatment, the diagnosis is put down as "syphilis of the lung." A close analogy is that of syphilis of the stomach, which is also a frequently made diagnosis. Cases are reported with gastric symptoms and a positive Wassermann reaction, and if under anti-syphilitic treatment the patient gets well, the diagnosis is made of syphilis of the stomach. I think the majority of us would say that syphilis of the stomach is probably one of the rarest lesions found on autopsy.

MALIGNANT TUMORS OF THE LUNG

A. V. ST. GEORGE, M.D.

(From the Pathological Laboratories, Bellevue Hospital, New York)

Primary neoplasms of the lung and associated structures have always been considered a great rarity. Isaac Adler, in 1912, called attention to an apparent increase in primary lung tumors and in the past year or two case reports have been noted more often in medical literature. The increase in the number of cases at Bellevue Hospital seems to bear out Adler's observation.

In Bellevue Hospital, during a period of ten years ending July, 1917, there were three primary lung neoplasms autopsied; from July, 1917, to July, 1919, there were two patients with new growths of the lung coming to autopsy. On the other hand, during a period of twenty months from July, 1919, there were autopsied one case of primary sarcoma of the lung, four cases of primary bronchial growths, one adenocarcinoma of the lung, and one adenocarcinoma of the lung arising from the smaller bronchioles. These seven cases have been made the subject of a paper to be published and are, therefore, merely abstracted here.

Case 1. A case of primary lung sarcoma, presented before this society in March, 1920 (published in the *Proceedings of the New York Pathological Society*, N. S., vol. 20, Nos. 1-5, January-May, 1920), and recorded as an alveolar lung sarcoma.

Case 2. The patient was a man forty-nine years of age, married, colored, a janitor by occupation, who was admitted to Bellevue Hospital on January 30, 1920, and died February 11, 1920. The onset of his illness occurred four weeks previous to admission, characterized by severe pain in the upper right part of the chest, in the infraclavicular region, of short duration but recurring at frequent intervals; the patient also suffered from severe dyspnoea for three weeks. The family history was irrelevant.

Physical Examination: The right eye was absent (removed seven years ago because of trauma); the left eye showed arcus senilis and the pupils reacted sluggishly to light. There was no marked asymmetry of the chest and no expansion on the right side. Dullness was present over the entire right lobe; there were no breath sounds and vocal fremitus was diminished. The left lung was resonant, the breath sounds normal, and there were a few sibilant râles at the base posteriorly. The apex of the heart was palpable in the fifth

space, 17 cm. to the left; there was no enlargement at the base. A long, soft systolic murmur was heard at the apex; the pulse was of poor quality. There were a few old scars present over the tibiae; knee jerks were not obtained. Thoracentesis showed bloody pleural fluid (not examined microscopically); the urine was normal and the sputum negative for tubercle bacilli; Wassermann reaction was negative. X-ray showed an effusion into the right pleural cavity. The temperature varied between 98.8° and 100° F.; respirations 24 to 32; pulse 80 to 120.

Diagnosis: Chronic endocarditis; myocardial insufficiency with decompensation.

Autopsy (abstract of protocol): The left lung was easily removed and was voluminous. The pleura was glistening and free from adhesions and exudate. The lung pitted on pressure and was cottony to the touch. It cut with difficulty and the cut surface was dry. The right lung was removed with difficulty due to fibrous adhesions which were especially firm posteriorly. Between the visceral and parietal layers there were about 200 c.c. of bloody fluid and partly clotted exudate, which showed a network of fine fibrin. The pleura was enormously thickened, dense and white. The lung was large, greatly increased in weight, solid and non-crepitant throughout. On section, the upper lobe contained a large, irregularly shaped tumor, which presented a variegated appearance, and was yellow, reddish-yellow and gray in color, extremely soft and friable. It bulged from the cut surface. The tumor occupied almost the entire upper lobe, there being only an area of about 1 to 2 cm. of lung tissue surrounding the tumor. This tissue was solid, non-crepitant and, on section, gray and rough, as was also that of the lower lobe. The alveoli on pressure exuded quantities of thick, cream-colored fluid. The bronchi were congested, but showed no other naked eye changes. The peribronchial lymph nodes were enlarged and, on section, showed a white friable tissue, probably metastatic tumor tissue.

Anatomical Diagnosis: Right lung—hemothorax; thickened pleura; fibrinous pleuritis; primary carcinoma of upper lobe; lobular pneumonia of lower lobe. Left lung—emphysema.

Microscopic Examination: Microscopically, the tumor in the lung showed small epithelial cells, fairly uniform in size, with many mitotic figures, solidly filling most of the lung alveoli; only here and there were there remains of unoccupied lung alveoli. Microscopic diagnosis: Carcinoma, arising from the alveolar epithelium of the lung.

Case 3. The patient was a man sixty-one years of age, Scotch, married, a carpenter by occupation, who was admitted to Bellevue Hospital on April 24, 1920, and died June 27, 1920. He stated that he had had a chronic winter cough for years; malaria twenty years ago; five years ago complete blindness, diplopia; influenza one year ago with sudden onset, pain in chest, fever, and cough for seven weeks. Marital history: wife and five children living, one child died in infancy, cause unknown. Habits: bowels regular, occasionally nocturnal urination is excessive; coffee taken, occasionally alcohol; tobacco; one pound per month. Family history: mother

and father dead, latter at ninety years of age; two brothers and one sister alive and well.

In the middle of December the patient began to cough and expectorate and feel tired. This progressed gradually until, at the end of February, he expectorated about one-half ounce of bright red blood. Thereafter he became very weak with pain in chest, and had to give up work; he was unable to stay in bed because of feeling of pressure and cough, and slept sitting up. There were constant knife-like pains in the left chest, exaggerated by cough and deep respiration; also anorexia and marked dyspnoea on exertion.

Physical Examination: The thorax was well developed and there was slight retraction of both clavicular fossæ. The apex beat of the heart was heard in the fifth space; there were no murmurs or thrills; the left border was not definable; pulses equal; arteries sclerotic. The lungs showed limited expansion on the left side; the left lung was flat throughout, no breath sounds or râles. The right lung was resonant; the inspiration exaggerated, and there were fine râles posteriorly during inspiration and large and fine râles anteriorly. Physical examination was otherwise negative. On May 10th, it was noticed that the veins of the upper part of the chest and neck were dilated; there were also marked cyanosis and dyspnoea.

Fluoroscopic examination showed the left side to be dense; there were mottled areas and extension of infiltration on the right side; the surface of the lung was extremely hard and nodular, and suggested a new growth. X-ray diagnosis: New growth.

The urine was negative; blood count showed white blood cells 13,000; differential count: polymorphonuclears 78 per cent., transitionals 11 per cent., eosinophiles 1 per cent., lymphocytes 5 per cent., large mononuclears 5 per cent.; sputum negative for tubercle bacilli on fourteen different occasions. The temperature varied between 100 and 101 and at one time rose to 102° F.; pulse 78 to 104; respiration 20 to 32. The patient lost nine pounds during his stay in the hospital (150 to 141 pounds). The Wassermann test was negative.

Autopsy: On opening the left pleural cavity, a large amount of dark, viscid fluid escaped. The lung was soft and densely adherent to the pericardium and to the chest wall. The organ could not be separated as a whole, but had to be torn from the chest wall and mediastinum in shreds. The lung was collapsed, soft, and everywhere contained nodules which varied in size from that of a small pea to about half the size of a hen's egg. The rest of the lung tissue was soft and pulpy, and there was very little evidence of air-containing tissue. The left bronchus contained two small nodules about the size of a pea, which extended into the lung. In the apex of the upper lobe there was an encapsulated mass, about 5 cm. in diameter, from which creamy pus was expressed. The walls of this abscess were made up of white, friable tissue. There was no evidence of other abscesses. The right lung was free in the pleural cavity, without adhesions, and was readily removed. On section, the greater part of the lung was air-containing, but throughout there were small, hard nodules

which varied in size from that of a pea to about half the size of a hen's egg. The intervening lung tissue was dark red in color but crepitant. The right bronchus showed no evidence of infiltration. The pleural cavity contained no fluid and no adhesions.

Anatomical Diagnosis: Lungs—carcinoma; chronic fibrinous pleuritis; atelectasis; abscess; acute bronchitis; carcinoma of bronchus (left).

Microscopic Examination: Microscopically the lungs showed large, pale staining cells, with prominent nuclei, appearing in cords or strands, and occupying the lung alveoli. There was but little of a connective tissue framework present. The nodules in the right lung were similar to those in the left. Microscopic diagnosis: Carcinoma arising from mucous glands of left bronchus.

Case 4. Adult male, fifty-one years of age, married, American, admitted to Bellevue Hospital September 9, 1920, died September 14, 1920. The patient stated that he had been engaged in newspaper work since he was twenty-one years of age; he smoked a moderate amount of cigarettes and took alcohol occasionally; he had measles and diphtheria during childhood; wife and one child alive and well.

The onset of the patient's illness occurred in February with grippe, at which time he was confined to his bed for one week. Since then, he suffered from cough, dyspnoea, pain in chest, chills, fever, and night sweats; lost weight and strength; moderate expectoration, anorexia, no hemoptysis.

Physical Examination: The patient appeared to be well developed and well nourished, but chronically ill. The lungs showed very little expansion on the right side; posteriorly vocal fremitus was absent from the midscapular region to the base; there was flatness over the same area and no breath sounds; above this area there was harsh breathing with few râles. Respirations were impaired at the apex on the left side and there were compensatory breath sounds throughout the left lung. The liver was palpable and there was a mass in the lower hypochondriac region, firm and slightly nodular, moving on respiration. Twelve hundred c.c. of blood-tinged fluid were removed from the right side on September 10, and 300 c.c. of similar fluid were removed from the left side on September 11.

X-ray examination showed the right chest to be apparently full of fluid; the left chest showed two rounded areas of consolidation; diagnosis, metastatic lung tumor. X-ray of the kidney showed nothing abnormal. On the day before death occurred, the patient became very weak, the pulse rapid and the temperature subnormal.

The sputum was negative for tubercle bacilli on three examinations. The pulse varied between 120 and 130; temperature 97° to 98° F.; respirations 24 to 34. The urine showed a trace of albumin and granular casts; Wassermann reaction negative.

Diagnosis: Carcinoma of stomach with metastases in lungs; tuberculosis; effusion on right side.

Autopsy: On opening the chest, the pericardium was pushed over to the left of the mid-sternal line. The right pleural cavity was filled with a sero-sanguinous fluid which had pushed the right lung (atelectatic)

into the cardio-hepatic angle. The excessive amount of fluid explained the descent of the diaphragm.

The left lung was removed easily, and was about normal in size. At the apex, however, there was a large, firm nodule, about the size of a plum. In the center of the upper lobe was a smaller nodule about the size of a walnut. The rest of the upper lobe was crepitant. In the lower lobe there was a hard nodule, about the size of a plum, but the rest of the lung was crepitant. On section, these nodules were composed of whitish, somewhat soft tissue, and had an irregular outline. The pleura was smooth and glistening.

The right lung was small and pushed into the cardio-hepatic angle. Only the periphery of the organ was crepitant and seemingly not involved. The inner half was made up of new growth. The mediastinal lymph nodes were involved and appeared as large, white conglomerate masses. These lymph nodes were so intimately associated with the tumor growth of the lung that lymph nodes and lung had to be removed en masse. The right pleural cavity contained about two quarts of sero-sanguinous fluid. The pleura was studded with cluster-like white growths, most marked on the lateral and diaphragmatic surfaces. The bronchus on the right side was thickened, white and of a fibro-cartilaginous consistence, and merged with the lymph nodes and extended into the lung.

The right kidney was of normal shape and size. The capsule stripped easily and exposed a smooth surface. Differentiation between cortex and medulla was well shown. The substance of the kidney was firm to the touch. The left kidney was about twice the normal size and to it was attached a large amount of fatty tissue. On section, the cut surface showed the medulla to be replaced by a mass of yellowish-white, soft material. The growth had infiltrated the upper pole, but in the lower part there was a zone of intact cortex. The capsule was so intimately attached to the growth that it was difficult to distinguish it and to peel it off.

Anatomical Diagnosis: Carcinoma of right lung with metastases in mediastinal lymph nodes, pleura, and left lung; atelectasis (right); hydrothorax (right); apical adhesions of left lung; metastatic carcinoma of left kidney.

Microscopic Examination: Microscopically, the lung tumor was similar in appearance to the one described in the last case. The kidney metastases in their morphology were similar to those of the lung. Microscopic diagnosis: Carcinoma arising from mucous glands of right bronchus.

Case 5. Adult male, thirty-eight years of age, Irish, married, electrician by occupation. Family history: father died as the result of an accident, mother of old age, one brother died of pneumonia and one sister during childbirth; one sister living. The patient stated that he drank tea and smoked tobacco excessively, but had not taken alcohol in eight years; he had gonorrhoea twenty years ago. His illness began on November 19, 1919, with cough and pain in right chest and thick yellowish expectoration. In December of the same year the sputum became streaked with blood; the expectoration was greatest in the morning. The patient lost considerable

weight (dropped from 175 to 145 pounds in four and a half months) and became pale.

Physical Examination: There was marked dullness over the upper third of the right chest anteriorly and from the apex to the spine of the scapula posteriorly. The chest was asymmetrical and there was diminished expansion of the right side. The percussion note was dull over the upper part of the right chest, and extending down to the second rib and behind to the spine of the scapula. The breathing was high pitched over this area and many coarse and fine dry râles were heard. The heart was situated in the third space, extending two and three-quarter inches to the right and two and one-half inches to the left. Fluoroscopic examination showed almost complete consolidation of upper half of right upper lobe, with a cavity about the size of a small onion situated anteriorly, about opposite the third rib, this cavity being partly filled by fluid. No physical signs of a cavity could be made out. The patient expectorated about four ounces of sputum per day. These symptoms continued, the patient losing weight rapidly. He had three severe attacks of pulmonary hemorrhage, succumbing to the last attack quite suddenly on October 8, 1920.

The sputum was examined fourteen times for tubercle bacilli with negative results. The urine showed a faint trace of albumin and an occasional granular cast. Blood count showed white blood cells 19,200; polymorphonuclears 82 per cent., transitionals 1 per cent., lymphocytes 14 per cent., eosinophiles 3 per cent. The temperature was 102° F. on admission, but remained normal during his stay in the hospital. The Wassermann reaction was negative on two occasions.

The patient was first seen in December, 1919, when fluoroscopic examination showed a small dense shadow at the hilus of the right lung, about 1.5 cm. in width by 4 or 5 cm. in length. Subsequent frequent fluoroscopic examinations showed this shadow to expand and cover the upper lobe as a more or less concentric mass, the shadow becoming darker as time went on.

Autopsy: On opening the chest, the left pleural cavity was normal. The right pleural cavity was almost completely obliterated by fibrous adhesions which were markedly firm and almost stony hard in the region of the upper lobe in the posterior portion. The thymus was replaced by fat.

The left lung in the gross was normal. The right lung was removed with difficulty and its surface was covered by fibrous bands. Along the upper lobe it had become a dense, white, almost calcific blanket. On section of the lung, two abscess cavities were found, one in the upper lobe, the other in the lower lobe. Both these abscess cavities measured, roughly, 8 to 10 cm. in diameter, though the one in the upper lobe was larger than that in the lower lobe. Both cavities contained a mass of blood clot. The cavity in the upper lobe situated near the lower margin was lined with a whitish flake-like substance, friable and easily removed. There was no firm delineating membrane surrounding either cavity. The remainder of the upper lobe was hard. On section, it was of a grayish, opaque appearance, and through it radiated massive streaks of fibrous tissue arising from a

dense white structure at the hilus. This firm mass was found connected with the primary upper right bronchus from which it apparently took origin. The bronchus was completely surrounded by tumor tissue and finally merged with it. The abscess in the lower lobe was situated near the upper portion and, except for blood clot, it contained nothing worthy of record. There was, however, very little odor to the organ. The lower portion of the lobe was slightly congested. The middle lobe was somewhat compressed and firmly bound to the upper and lower lobes by dense adhesions. The branches of the bronchi contained blood clot and were streaked with blood. Hemorrhagic foci in the abscesses could not be determined.

Anatomical Diagnosis: Epithelioma of lung and bronchus (right); abscesses of lung (secondary); chronic interstitial pneumonia; chronic adhesive pleuritis; pulmonary osteo-arthritis.

Microscopic Examination: Microscopic sections taken from several areas of the lung and bronchus showed a very cellular, squamous cell tumor in which there were typical pearl formations. Microscopic diagnosis: Epithelioma of right lung arising from the right bronchus.

W. G. MacCallum (*Text-Book of Pathology*, p. 961) refers to a series of primary lung tumors, among which were several instances of a large cavity in the lung, lined by opaque, yellowish-white, friable, crumbling tissue, in some of which the bronchus could be traced directly into the cavity, its wall becoming thickened by a new growth of the mucosa, which became continuous with the margins of the lining of the cavity. Microscopically, the tumor was made up of strands of atypical stratified epithelium, showing all the characteristics of cutaneous cancers. MacCallum believes it may be an example of metaplasia, but also suggests that it may be dependent upon an embryonic displacement of cells destined to become squamous epithelium. These tumors seem to be in accordance with the one which we encountered.

Case 6. Adult male, forty-one years of age, married, a packer by occupation, admitted to Bellevue Hospital April 3, 1920, died June 18, 1920. The patient's father died at the age of sixty, cause unknown; mother died at fifty-five of stomach trouble; two sisters died at the ages of twenty-seven and twenty-nine, respectively, cause unknown. Previous history—the patient had had measles, pertussis, bronchitis, scarlatina; in adult life, recurrent bronchitis; operative—circumcision and varicocele; had gonorrhœa at the age of twenty, no lues. Habits: drank coffee, tea, whiskey and beer; bowels regular; nocturia for past three or four years.

The onset of his illness occurred in December, 1919, with pain in the right chest posteriorly, in the scapular region; was strapped by a doctor and told to go back to work. Two weeks later, he stopped work again and rested for three weeks on account of pain in chest, fever, and cough with expectoration. His sputum was examined on three occasions and found negative for tubercle bacilli. At the end of three weeks, he felt better and returned to work for two days, when symptoms recurred, and then he noticed swelling of the veins of the neck. He went to a hospital, remained there forty-seven days, and was then referred to Memorial Hospital for treatment of tumor of chest. X-ray at the first hospital was negative for new growth. Dyspnoea became gradually marked, also headaches, vertigo with coughing and numbness and tingling in left arm after violent coughing. He lost about twenty pounds in weight in four months.

Physical Examination: There was no cyanosis or dyspnoea in the recumbent position. The veins of the neck, back and arm were dilated and prominent. There was no limitation of expansion of the lungs and tactile fremitus was diminished at the right base posteriorly and laterally. There was flatness over the same area, and harsh vesicular breathing at the right apex posteriorly, just above the area of flatness. The breath sounds were broncho-vesicular, almost bronchial, and were absent at the base. Normal vesicular sounds were heard over the left chest. Heart—apex beat not visible; faintly palpable with point of maximum intensity in the fifth space, three and three-quarter inches from mid-sternal line; no thrills; no enlargement by percussion; no murmurs; pulses regular. The abdomen was negative on external examination. The axillary and right cervical lymph nodes were palpable. On May 20, 100 c.c. of clear straw-colored fluid were removed from the right chest; on June 6, 125 c.c. were aspirated and on June 17, 625 c.c. of reddish clear fluid were removed (sp. gr. 1.018, much fibrin). On May 27, right hemiparesis was noted, also slight motor aphasia. On June 15, the patient became drowsy, but was still rational, with frequent hiccup.

Three X-rays were taken; the first showed pleural effusion (4/9/20); the second, interlobar abscess between right upper and middle lobes, effusion in right costo-phrenic space (5/17/20); the third, new growth of lung with pleural effusion, no metastasis in bony skull.

The urine was negative; Wassermann reaction on blood and spinal fluid negative; colloidal gold reaction on spinal fluid negative. The temperature varied between 99.8° and 102° F., averaging about 101°; respirations 18 to 32; pulse 88 to 120.

On June 18, the patient died.

Autopsy: The right pleural cavity was distended by pale brownish-colored fluid in the form of pockets. The right lung was everywhere firm to the touch and it was chiefly adherent over the sides. The costal pleura was thickened and on the pleura near the sixth and seventh ribs there was a firm tumor mass, whitish in color, measuring about one inch in diameter. The right bronchus was everywhere infiltrated with firm, white tumor

growth. The upper lobe was bluish red in color and presented a number of what appeared to be abscesses of smaller size. The lower lobe contained in its center a considerable amount of softened, whitish material, resembling the appearances of a lung undergoing resolution. The left lung showed compensatory emphysema and the upper lobe was large and extended somewhat over the middle line. Section presented no other appearances than that of congestion; the bronchi were normal in appearance except for congestion of the mucous membrane.

Anatomical Diagnosis: Primary tumor of right bronchus with metastases in right cerebellar lobe and right kidney.

Microscopic Examination: Microscopically, the tumor, as well as its metastases, presented large, clear, pale staining cells, similar to those found in the above described bronchial growths. Microscopic diagnosis: Carcinoma of right bronchus.

Case 7. The patient was a woman sixty-six years of age, who was admitted to Bellevue Hospital February 9, 1921, and died February 27, 1921. She stated that she had lost considerable weight during the past year (exact amount not known); appetite was poor, and bowels constipated. She also stated that she had been operated on for cystocele (date not given). The onset of her illness occurred four weeks previous to admission to the hospital, characterized by pain in the left side of the chest, with coughing and gradual loss of strength and weight. Associated with this condition she developed edema of the lower extremities with some arthritis of the left hip; she expectorated small amounts of dark rusty sputum.

Physical Examination: Revealed an elderly female, weighing about 110 pounds, poorly developed and nourished. The skin was dry and scaly; no palpable adenopathies; marked anæmia. The pupils reacted to light and accommodation. The patient held her head forward as though too weak to support it and there seemed to be some separation between the seventh cervical and first dorsal vertebræ. The thorax was poorly developed and no apex beat was visible. There was some dullness with increased breath sounds over the left upper lobe and crepitant râles over the right middle lobe anteriorly and in the left axilla in the fifth and sixth interspaces. The heart was not enlarged; there were no murmurs; the sounds were distant and of poor quality and the vessels sclerosed. The liver was felt two fingers' breadths below the costal margin; the spleen and kidneys were not palpable. There were no varicosities or ulcers of the lower extremities; the knee jerks were normal; no Babinski or Oppenheim. On February 10, many crepitant and subcrepitant râles were noted, with dullness and distant bronchial breathing over the left infraclavicular region, and on February 26, there was consolidation of the left lobe.

The urine was amber-colored, sp. gr. 1.010, reaction acid, albumin faint trace, glucose negative, granular casts, few red blood cells. Blood count: Leucocytes 6,800, number of cells counted 50, polymorphonuclears 70 per cent., transitionals 3 per cent., lymphocytes 27 per cent. The Wassermann reaction was negative; the sputum was negative for tuberculosis. The temperature was 101.6° F. on admission and varied between 98.4° and 103.4°. The pulse varied between 110 and 140.

Clinical Diagnosis: Chronic interstitial pneumonia.

Autopsy: On opening the chest, the precordial area appeared normal in size, the right border being overlapped by the edge of the right lung. The right pleural cavity had scattered strands of loose fibrous adhesions over it. The left pleural cavity had many easily broken down adhesions extending over the upper lobe. Both cavities were dry.

The lungs did not collapse completely when removed. The surface of both lungs presented a lobulated appearance. Smoothly rounded lobules, 1 to 3 cm. in diameter, were marked off by deep fissures so that the appearance was similar to that of a hobnailed liver with very large knobs. This lobulation extended throughout practically the whole of both lungs, but was less marked at the extreme base. The lungs were heavy and felt moderately firm, except for the extreme right base and the lower third of the left lobe. Each individual lobule had superficially the light cottony feeling of the emphysematous lung, but on deeper pressure, firmer tissue was felt. The surface was light gray and mottled with anthracotic pigment. The pleura, except in the fissures described, had a smooth glistening appearance but not on the right diaphragmatic surface, and between the right middle and lower lobes. Here it had lost its luster and there was an adherent exudate of greenish fibrin. On section, the lung presented a dirty gray appearance, imperfectly aerated, and a number of dilated spaces containing greenish-yellow pus. These were lined by a definite membrane, and one or two admitted a probe for some distance, suggesting that they were bronchiectatic. The smaller bronchi exuded pus on pressure.

The liver was normal in size. The capsule was thin and tense and somewhat adherent to the diaphragm and transverse colon. One fibrous nodule, about 0.5 cm. in diameter, was visible beneath the capsule on the anterior surface. On section, it cut with resistance and extended into the liver tissue.

Anatomical Diagnosis: Right lung: organizing pneumonia; adenocarcinoma; acute fibrinous pleuritis; bronchiectasis; emphysema; purulent bronchitis. Left lung: fibrinous pleuritis; interlobar empyema; purulent bronchitis; bronchiectasis; emphysema; organizing pneumonia; adenocarcinoma. Liver: corset liver; metastatic nodule (adenocarcinoma); perihepatitis.

Microscopic Examination: Sections from the lung showed a fibrous tissue hyperplasia in places, together with many areas of prominently defined epithelial growths scattered throughout both lungs. Microscopic diagnosis: Carcinoma arising from the finer bronchioles in the lung.

The diagnosis of primary lung tumors presents one of the most interesting as well as one of the most difficult problems in clinical medicine. The possibility of metastases from a symptomless growth in an esophageal diverticulum or a small growth in the gall-bladder, thyroid, etc., is always well worth considering.

No positive diagnostic criteria are known. Frequent examinations with the fluoroscope are most apt to reveal a progressive growth.

Discussion:

DR. LARKIN: It is difficult to discuss primary tumors of the lung. One of the present specimens is a large tumor centrally located which has all of the characteristics of tumors which are primary in the bronchi. The other specimen seems not to be connected with the lung, but is a tumor which is invading the lung secondarily and is primarily a pleural neoplasm. It has that very peculiar character of incrusting the pleura, sending ramifications into the lung and along the bronchi. These tumors are interesting, not only because of their pathological rarity, but also because of the clinical phenomena during the life of the patient. I have in my collection six or eight tumors like the specimens shown here, and the more I have studied the histology of the type of tissue in order to arrive at a conclusion as to where the tumor originated, the more I am bewildered. The tumor, with the incrustation, seems to me to be a tumor primary in the pleura, for it has the physical characters of ramifications and the incrustation of the pleura and the involvement of the bronchi. These tumors may be diagnosed from physical evidence during the life of the patient, for they are usually accompanied by large amounts of pleural exudate, generally hemorrhagic in type. A number of years ago Dr. Ewing made a diagnosis of primary endothelioma of the pleura from a centrifugalized exudate. Only recently I have seen a case in which a large amount of hemorrhagic fluid was withdrawn from the pleura and on examination of the centrifuged sediment there was no question of the diagnosis of endothelioma. At autopsy a tumor of the right lung was found, which is exactly similar to the specimen shown here to-night.

DR. MOSHCOWITZ: I do not think the diagnosis of primary tumors of the lung is quite as difficult as Dr. St. George makes it out. The majority of tumors of the lung seem to be of three types: first, those that resemble mediastinal tumors, and I think these are mostly primary tumors at the hilus of the lung arising from the bronchus. I should like to call attention to an early and characteristic sign, and that is the fixation of the trachea. It has very little lateral and vertical mobility. The second form in which tumors of the lung may present themselves clinically is that where you find a solid mass situated in one or the other lung. The third type simulates pleurisy with effusion and this is the one which I think offers the most difficult problem in diagnosis. I find that you can often make a diagnosis much better by taking the centrifugalized fluid, fixing it in formalin so that it comes out a gelatinous mass from the bottom of the test tube, and running it through paraffine. The chances of finding tumor cells are far better than by simply making a smear.

DR. EWING: This winter I have seen at autopsy two cases of epithelioma of the lung arising on tuberculous bronchitis—highly malignant squamous

carcinomas. The proportion of cases Dr. St. George found free from tuberculous lesions is unusual. I wonder whether he has thoroughly searched the tissues for tuberculous lesions.

DR. LARKIN: Do I understand Dr. Ewing to say that there is a connection between tuberculosis of the peribronchial tissues and the malignant growths?

DR. EWING: In these cases there were active tuberculous lesions in the lungs from which the epithelioma developed.

DR. LARKIN: Were the tumors of any great size?

DR. EWING: No.

DR. LARKIN: Was the diagnosis macroscopical or microscopical?

DR. EWING: Both.

DR. ST. GEORGE: In answer to Dr. Ewing's question as to whether we searched the tissues for tuberculosis, we did. The only one that showed any evidence of tuberculosis was the sarcoma case and that had some nodules at the apex.

As regards the diagnosis of these tumors, I do not want to convey the impression that it is so exceedingly difficult, although to differentiate a primary lung tumor from a metastasis is difficult to some extent. Recently at a meeting here in New York a clinician said he had diagnosed thirty lung tumor cases, but all without an autopsy; hence whether they were correct diagnoses is a debatable question. We have presented only those cases of primary lung tumor which can be proved beyond doubt to be so. Dr. Norrie has seen a number of these cases at the hospital and even in the patient where the shadow was observed growing from the lung he was not willing to make a diagnosis of tumor, but held to his diagnosis of abscess. He would not say whether they were primary lung tumors, or were metastatic. In the autopsy service at Bellevue the percentage of tumors metastasizing into the lung is rather large, and we hesitate to make a diagnosis of primary lung tumor.

I do not know which specimen Dr. Larkin referred to as being an endothelioma, but I believe it is the one which I had seen six weeks after onset of symptoms and which showed the shadow at the hilus. I knew the man very well and followed him up. In another hospital they had made a diagnosis of tuberculosis in his case, largely I believe because they obtained a +++ tuberculous complement fixation. I had him fluoroscoped repeatedly during the following months, and we found the shadow to grow out and into the lung. I think it is fair to assume that it is a bronchial growth. Some of the sections are suggestive of the tumor starting from the glands of the bronchus.

THREE BRAIN TUMORS

NATHANIEL B. STANTON, M.D.

(From the Laboratory of the Lenox Hill Hospital, New York City)

In his text-book on Neoplastic Diseases, Ewing states that probably one per cent. of all deaths are due to brain tumor, while Tooth in an analysis of 632 cases gives as the relative frequency in location: tumors of the brain proper 94 per cent., of the pituitary 2 per cent., and of the pineal gland less than one half of one per cent. Based on an analysis of 434 cases, the frequency of various histological types is tubercle 183, gumma 45, sarcoma 113, glioma 127, osteoma 4, and cholesteoma 2.

The cases recorded in the present report are of the pituitary and pineal glands. Of the various histological types encountered in the pituitary gland the order of frequency is diffuse hyperplasia with focal adenoma, adenocarcinoma, and last sarcoma. An analysis of sixty-eight cases of pineal tumor gives as the most common types in the order of frequency: cysts either with or without tumor growth, teratomata, and finally ependymal glioma.

The general symptomatology of cerebral neoplasms may be considered under three headings: (*a*) symptoms common to all tumors, such as headache and evidence of increased intracranial pressure; (*b*) localizing symptoms, such as paralysis; (*c*) symptoms due to disturbance of special function associated with neoplasms of the pituitary and pineal glands.

The special symptoms arising from neoplasms in the pituitary may be divided into two groups: (1) the cephalic type, in which pressure symptoms are predominant; (2) the dystrophic type, in which disturbances of growth are prominent symptoms. In the cephalic type the chief complaints are headaches, dizziness and paralyses, or interference with other portions of the visual apparatus. The dystrophic type may again be divided into four groups: giantism with or without acromegaly, infantilism, acromegaly, and that condition spoken of as adiposis genitalis.

The tumors of the pineal gland show as endocrine disturbances: hypertrophy of the sexual organs, overgrowth of the pubic hair, and precocious sexual instinct.

The first case, that of a pituitary carcinoma, has the following history. A male, age sixty-two years, complained of severe pains in the abdomen lasting for the past six weeks. This pain was continuous, burning in nature and did not radiate; it was made worse by eating and was not relieved by vomiting. There was no hematemesis. There were also present a slight cough and considerable loss of weight. He had had severe headaches and a ptosis of the right eye for three weeks, and a ptosis of the left eye for a short time about five weeks previous to admission.

Physical examination showed the following pathological conditions: emaciation; the right pupil dilated, irregular and sluggish in reaction; a divergent squint; diplopia; and atrophy of the optic nerves. During his illness all ocular nerves except the external rectus of the left eye became paralyzed. There was a palpable tumor mass in the left upper quadrant of the abdomen. The abdominal and cremasteric reflexes were absent and there were shooting pains in both legs.

FIG. 1.

X-ray examination showed erosion of the sella turcica and destruction of the clinoid processes, and in addition a large, dense, irregular consolidation at the root of the right lung which increased in size very rapidly as shown by later pictures. Further radiographic examination showed a constant deformity in the prepyloric region of the greater curvature of the stomach. Gastric analysis showed an absence of free hydrochloric acid and a total acidity of nine. The blood sugar was 81 milligrams per 100 c.c.

The unusual features found at autopsy were several. At the hilus of the right lung there was an irregular neoplasm which involved the large vessels and the main bronchi and which measured 13 cm. in the greatest

diameter. The central portions of the growth were necrotic. All of the mediastinal nodes were involved in a neoplastic process and matted together the lungs and heart. The head and the larger portion of the body of the pancreas were replaced by neoplastic tissue. There were several metastases in the mesentery and omentum, the largest measuring 8 cm. in diameter. In the mucosa of the stomach at the greater curvature near the pylorus, there were three metastases, the largest of which was a sessile mass 3 cm. in diameter. Both adrenals showed metastatic deposits and there were growths in the spleen and in one kidney, as well as several neoplastic deposits in the skin and subcutaneous tissue.

FIG. 2.

The convolutions of both hemispheres of the brain were markedly flattened and the pia arachnoid showed a marked edema. In the region of the pituitary gland there was a soft mushy neoplasm which had very extensively eroded the sella turcica, and which was tightly adherent to the bone and meninges and which by direct extension had invaded the optic commissure. Both lateral ventricles were much distended and contained excessive amounts of fluid. In the position of the third ventricle (Fig. 1) there was a dark, red, smooth, globular mass, 4 cm. in its greatest diameter and which had a sessile base. Section through the mass showed that the base extended through the brain and was continuous with the neoplasm involving the pituitary gland.

Microscopic examination showed the tumor to be a small cell epithelial neoplasm (Fig. 2) whose architecture, particularly in the primary growth in the pituitary, was that of a papillary form, the cells being about a center core consisting of a thin-walled blood vessel supported by a loose connective tissue. Areas of necrosis were relatively common. In sections through the pituitary the gradual transformation from the normal cells of the pars anterior to frankly malignant cells was demonstrable.

The interesting phases of the case were the absence of evidence of disturbed endocrine function, the widespread metastasis, and the absence of disturbances in sugar metabolism as evidenced by a normal blood sugar and absence of sugar in the urine, this in spite of widespread lesions, which involved pancreas, adrenals and pituitary.

The second case of pituitary tumor, also a carcinoma, occurred in a male aged eighteen years. He was admitted to the hospital because of persistent headaches, gradually developing blindness and paralysis of the third and ocular branch of the fifth nerves on the right side. There was somnolence and loss of weight. The X-ray examination showed no erosion of the sella turcica. The evidences of disturbed endocrine function were emaciation, absence of axillary hair, poorly developed genitalia, a fine smooth skin and the general appearance of a youth about five years younger than his given age.

FIG. 3.

Upon opening the skull a large amount of clear cerebro-spinal fluid escaped. The convolutions of the right forebrain were found to be markedly flattened. The pituitary was replaced by a soft hemorrhagic mass which had almost completely destroyed the clinoid process of the right side and had eroded the saddle of the sella turcica so that there was an opening into the sphenoidal cells (Fig. 3). The mass was tightly adherent to the me-

ninges and measured 2.5×1.75 cm. Both lungs showed small hemorrhagic infarcts. The testes were atrophic. The other organs were of no particular interest.

The microscopic examination of the second tumor showed a carcinoma of the alveolar type (Fig. 4) though the individual cells were of the same

FIG. 4.

general character as the first tumor described. The alveoli were of varying size and while in some areas definite lumina were demonstrable, in others cellular proliferation had filled the lumina. There were extensive areas of hemorrhage and smaller areas of degeneration.

In marked contrast to the first case, the second instance showed no metastasis and gave evidence of endocrine disturbance.

The third case of this series was a multiple cyst of the pineal gland discovered accidentally at autopsy and giving rise to no symptoms during life. A male, twenty-six years of age, complained of pain in the back of the neck and shortness of breath for five weeks. The pains were throbbing, radiated to the occipital region and kept him awake at night. At the same time there were stinging pains in the fingers and toes which lasted from

a few hours to a few days. There was no evidence of endocrine disturbance in either history or physical examination.

Physical examination showed a heart enlarged downward and to the left; a double mitral murmur at the apex and a diastolic murmur at the aortic area transmitted to the vessels of the neck. There were petechiæ in the conjunctivæ and skin and a blood culture showed *streptococcus viridans*. During his stay in the hospital he ran a septic temperature.

At autopsy the clinical diagnosis of malignant endocarditis was confirmed. The present interest is in the brain which was normal except for a small tumor of the pineal gland, 1.5 cm. in diameter (Fig. 5).

FIG. 5

Microscopical examination of the pineal growth showed a somewhat distorted and persistent pineal gland with foci of calcification and larger and smaller cyst cavities either lined directly by the normal pineal cells, or lined by a moderately thick layer of glia tissue.

The three cases have been presented not so much for their relative rarity, but as illustrations of the extensive neoplastic destruction which on occasion may occur in one of the endocrines without giving rise to the conditions usually associated with endocrine dysfunction.

Discussion

DR. EWING: I would like to ask what was the structure of the abdominal and other metastases in the second case. It is very rare to have so many metastases from pituitary tumors.

DR. ROHDENBURG: The morphology of the metastases was the same as that of the original tumor. Metastases were present in practically every organ of the body.

DR. EWING: Was the structure of the pituitary tumor characteristic of any you have seen before in the pituitary?

DR. ROHDENBURG: The morphology of the primary tumor was typical of other pituitary tumors which I have seen.

FIBRO-SARCOMA OF THE APPENDIX

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(From the Pathological Laboratory, Lenox Hill Hospital, New York City)

While epithelial neoplasms of the appendix, even though they are seldom clinically malignant, are not infrequent, neoplasms arising in the other types of tissue present in the organ are relatively rare. If chronic irritation is the important factor in tumor genesis, as is currently supposed, it would not be at all strange to see malignant change in the organ, for in relatively few individuals is there absence of evidence of chronic inflammation. Possibly the apparent rarity of clinically malignant tumors in this situation may be explained by the fact that in the vast majority of cases the chronic inflammation becomes acute and the offending focus is removed, either before the cancer age or before the irritation has persisted for a sufficiently long period.

The present case is that of a male, aged seventeen years, admitted to the hospital on the service of Dr. George Semken. His family history was strongly tubercular, and the patient himself stated that three months before admission he suffered from a cough, was feverish, and had profuse night sweats. With the exception of his cough the symptoms remained and two weeks before admission he noticed a mass in the region of the appendix. The only clinical and laboratory data of positive nature were the presence of a rounded mass, freely movable, in the region of the appendix, a septic type of temperature, and a radiographic finding that the tumor was attached to the cæcum. Tuberculosis could not be demonstrated either radiographically in the lungs or by various laboratory examinations. At a laparotomy a rounded, reddish tumor was found attached to the cæcum where the base of the appendix should have been, the omentum being attached to the edge of the tumor. The growth was extremely vascular, receiving its chief nutrition from the omental attachment.

The tumor measured 13 x 10 x 12 cm. and, as previously stated, attached to one surface was a broad band of omentum containing many large-sized blood vessels. At the other pole projected the lumen of the appendix which was patent throughout.

Microscopically the tumor was found to be composed largely of small spindle-shaped cells embedded in a fibrillar matrix (Fig. 1), which was scanty or fairly abundant and richly infiltrated with small round cells.

Spindle cells were fairly numerous and were spread diffusely throughout the tumor or arranged in parallel or interlacing bundles. Among these

FIG. 1.

cells were a few larger cells of round or spindle shape with hyperchromatic nuclei and acidophile protoplasm. The tumor contained many small blood vessels and capillaries.

The case is interesting from the standpoint of diagnosis, for with a familial history of tuberculosis, an onset of distinctly tubercular type and a mass in the ilioæcal region, the differential diagnosis between ilioæcal tuberculosis and neoplasm was not easy.

A TUMOR OF THE LEFT AURICLE

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The rare incidence of primary tumors of the heart is illustrated by the fact that in 3,000 autopsies at Nüremberg, Thorel did not encounter a single one; the Bellevue Hospital records of over 7,000 autopsies include no cases.

One of the first collections of primary tumors of the heart was made by Berthenson, who, in 1893, reported 28 cases of the following varieties: sarcoma 9, myxoma 7, fibroma 6, carcinoma 3, lipoma 2, cyst 1. As to location, 7 were in the right auricle, 3 in the right ventricle, 7 in the left auricle, 5 in the left ventricle, and 4 in the septum.

Link, in 1909, collected 91 cases; on some of them, however, the data were scanty, so that all may not be authentic. Myxomata and sarcomata are the most frequent cases in his series. In addition to this series, 11 cases of rhabdomyoma were collected by Wolbach in 1907.

Karrenstein's collection, in 1908, included 39 cases, excluding myxoma, and 38 cases of myxoma. This collection is of interest in regard to the location of the tumors. He finds that in the case of myxomata the left auricle is the most frequent site, while out of 6 cases of sarcoma 5 were located in the right side of the heart.

According to recent literature, the myxoma is the tumor of far the most frequent occurrence. A case of this tumor was reported before this Society by Louria in 1917. Thorel believes many of these reported as myxomata are in reality thrombi that have undergone myxomatous degeneration. He likewise rejects many reports of fibroma as being organized thrombi.

The first case of primary sarcoma was reported in 1865 by Bodenheimer. This case had been observed clinically and brings up the interesting question of the diagnosis of cardiac tumors.

No cardiac neoplasm has thus far been diagnosed during life. The diagnosis in this case most nearly approached a correct one. It was: "Cardiac disease of unknown origin."

The reason for the difficulty in diagnosis lies in the fact that there are no symptoms characteristic of cardiac tumors, but these resemble the symptoms of any form of cardiac disease and their character depends upon the size and location of the tumor. It has frequently been observed that there may be no symptoms referable to the heart, and the condition is discovered unexpectedly at autopsy. A number of writers have cited symptoms which they believe should be suggestive of a tumor of the heart. Thus Fraenkel considered bloody pericardial effusion, in the absence of tuberculous or scorbutic disease, a certain sign of cardiac neoplasm. This has, however, not been observed in any cases other than his own. Berthenson (1893) lays emphasis on embolic manifestations, but others consider these unusual in cardiac neoplasms. He also discusses murmurs, which may or may not be heard, and which, if present, may not be so clear as in endocarditis and may vary in intensity. Others mention exclusive involvement of one side of the heart.

The case to be presented tonight is as follows:

H. F., a male, thirty-seven years old, was operated on at Bellevue Hospital for inguinal hernia on January 18, 1921. He had never had symptoms referable to the heart and had an entirely negative medical history. On questioning, after cardiac signs were discovered, he said he had had rheumatism in the wrists several years ago. Examination of the heart showed enlargement to the left and rough apical presystolic and diastolic murmurs were heard. Compensation was so good that general anæsthesia was not contraindicated. The patient was discharged February 12, cured of the hernia, and was referred to the cardiac clinic. After he left the hospital, his feet became swollen and he was somewhat dyspnoëic. He came to the cardiac clinic and was referred to the ward on March 15. The patient became rapidly more dyspnoëic and cyanosis appeared. The respirations were 40. There was ascites, tympanites and edema of the feet and legs. Leucocytosis and fever were present.

Physical examination showed a well-developed man, dyspnoëic but lying flat in bed. Examination of the heart showed moderate enlargement to the right and left, with the apex beat in the fifth interspace outside the mid-clavicular line. The heart sounds were of fair muscular quality, irregularly irregular, rate 140. A systolic murmur was heard at the apex and a diastolic

murmur at the base and in the aortic area. The diagnosis was (1) chronic cardio-valvular disease with mitral stenosis and insufficiency and relative aortic insufficiency, (2) cardiac hypertrophy and dilatation, (3) au-

FIG. 1.

ricular fibrillation, (4) congestion, bases of both lungs, (5) chronic passive congestion of the liver, (6) coronary sclerosis and thrombosis with myocarditis, (7) ascites.

The morning after admission, at about eleven o'clock, the patient went into shock. The extremities were cold and blue, with drenching perspiration. The temperature was elevated; the pulse was not palpable at the wrist, and respirations were rapid and labored. The patient died suddenly, growing very blue just before death. The first heart sound was of good force and muscular quality within ten minutes before his sudden death.

The autopsy was performed a few hours after death. The main anatomical diagnoses were as follows: Tumor of left auricle, verrucous endo-

carditis of mitral valve, cardiac hypertrophy and dilatation, chronic fibrinous adhesive pleuritis, chronic passive congestion of the liver, fibroma of the left suprarenal gland, ascites, edema of lower extremities.

The pericardium was normal and contained no excess of fluid. The heart was moderately enlarged, especially the right ventricle. The right auriculo-ventricular orifice admitted three fingers easily. On exploring the left auriculo-ventricular orifice, it was found to admit only one finger, and a smooth, rounded body, slightly movable, was felt at the side of the orifice. On opening the heart, the valves of the right side and the aortic valves were found to be normal and there was no change in the endocardium. There was slight thickening of the walls of the right ventricle and dilatation of both ventricles. There were no changes in the coronary arteries. The mitral valve showed some thickening of the posterior cusp and of the attached chordæ tendineæ. The anterior cusp showed numerous small, somewhat flat, reddish, verrucous growths.

Attached to the antero-lateral wall of the left auricle was a firm, whitish mass, the size of a hen's egg. This was attached to the auricular wall for all except the lower 2 cm. of its length. The whole mass was 7.5 cm. long and 5 cm. wide at its widest part, which was about the middle. It was irregular in contour, smooth, but not glistening. The endocardium appeared to extend for about 4 mm. up the side of the mass. The lowest portion, which had no direct attachment to the auricular wall, projected into the auriculo-ventricular opening and was the rounded body felt on exploring the orifice before the heart was opened. It could be rotated slightly and in the formalin-hardened specimen is to be seen displaced upward and laterally. There was a band of rough reddish material, apparently fresh thrombotic deposit, separating the lower portion from the main body of the growth.

The mass was considered as probably a thrombus, with the possibility of its being a tumor.

Microscopic examination of sections removed from the mass in the left auricle revealed the fact that it was divisible into three zones. The lowermost zone was composed of apparently well-preserved heart muscle, superimposed upon which and constituting a second zone was a layer of fibrous tissue. The third zone presented a rather complex histology. Just above the connective tissue septum were masses of spindle-shaped cells which were arranged in whorls or bundles and which were indistinguishable from smooth muscle cells. These gradually faded into areas where all normal cell relationships were lost, the cells being irregular in arrangement and variable in size, provided with very little intercellular substance, the nuclei more or less richly chromatic, in places hyperchromatic, the whole representing, apparently, sarcomatous transformation of the supporting connective tissue. In some of the sections cells of this general type were found scattered around slit-like formations representing, possibly, dilated capillary vessels. In one of the sections, also, was a small collection of cartilage cells, some of which were evidently undergoing calcification. The presence of cartilage cells suggests the possibility that the tumor is teratomatous in nature.

Moreover, it is difficult to account for the presence in the growth of smooth muscle cells except on a developmental basis, unless one assumes, of course, that they are derived from the muscular layer of the nutrient arteries of the heart.

As stated above, the first case of primary sarcoma of the heart was reported in 1865. In 1910 Baldwin collected seventeen cases which he considered authentic, including one of his own. In 1918 Perlstein reported a case of sarcoma apparently originating from the epicardial areolar tissue. He had made a careful search of the literature, and enumerated thirty cases beside his own, omitting all those whose true sarcomatous nature appeared to him to be doubtful.

There are three interesting points in connection with the present case:

1. It illustrates the difficulty in distinguishing between a thrombus and a cardiac tumor without careful microscopic examination. The appearance of the tumor is that of a thrombus and, indeed, it consists in large part of thrombus which has been deposited on the tumor.

2. The location in the left atrium is unusual in this type of tumor. In Perlstein's thirty cases eleven were situated in the right atrium. The septal wall of the atrium is also a much more frequent site of attachment than the antero-lateral wall, which was the attachment in the present case. The septal wall is considered as having a disposition to tumor formation, perhaps from the complicated foldings and displacements which take place in development at this place (Marchand and Fuhrman).

3. The fact that the tumor projected through the mitral orifice, partially occluding it and giving rise to symptoms of mitral stenosis, is of great clinical interest. Link gives fourteen cases of cardiac tumor in which the mitral orifice was thus obstructed. In one case death was thought to be due to incarceration of the tumor in the orifice. Considering the sudden death, with extreme cyanosis just before death, such a mechanical factor may have been responsible in the present instance. Symptoms of both mitral stenosis and insufficiency were given by most of these tumors, and these were present in this case.

A case of this sort on which there was extensive clinical observation was reported by Pavlowsky in 1893. One of the most interesting facts in connection with this case was the observation that when the patient was lying down the signs were those of mitral insufficiency, while when she was examined sitting up signs of mitral stenosis were found. The patient could hardly be persuaded to assume a sitting position and was evidently in much greater distress than when lying down. At autopsy a tumor of the left auricle was found which, in the vertical position, would occlude the mitral orifice, giving rise to serious stenosis, and in the horizontal position would recede slightly, relieving the stenosis, but interfering with closure of the mitral flaps, thus causing insufficiency.

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Discussion:

DR. PAPPENHEIMER: I should like to ask whether the smooth muscle fibers which normally are found beneath the endocardium might not be a theoretical source of origin for the muscle fibers which enter into the composition of the tumor; also whether the auricular muscle had been invaded by the growth.

DR. HOFFMAN: No; there was a band of connective tissue between the muscle wall and the tumor.

DR. EWING: I would like to know what the histological diagnosis in this case is.

DR. HOFFMAN: It is sarcoma of the left auricle.

DR. SYMMERS: In view of the fact that cartilage and smooth muscle cells are present, one must consider the possibility that the tumor is a teratoma. But, as Dr. Pappenheimer has already suggested, it is likewise possible that the smooth muscle tissue represents a normal structure. It seems to me that the more probable diagnosis is that of sarcomatous transformation of the connective tissue stroma of a fibromyoma.

DR. EWING: It is much more cellular than any of the tumors of this

sort that I have ever seen, and I think on that account it is a very important case, because it gives a much better opportunity to determine the nature of these tumors than we ordinarily have. Most of them are very edematous so that the original structure is obscured. Here we have a well-nourished, large, solid tumor, from which I think it ought to be possible to come to some definite histogenetic diagnosis. My single glance at the specimen suggests two possibilities which I hesitate to mention after such a brief study—myosarcoma or neurogenic sarcoma. It might be worth while to try to demonstrate neuroglia fibrils by special stains.

DR. HOFFMAN: I ought to mention that probably the largest bulk of the tumor is composed of thrombus, so it may really be a small tumor with large deposits of fibrin.

TWO CASES OF CONGENITAL LESIONS OF THE HEART

ALEXANDER FRASER, M.D.

These cases, though showing a number of developmental defects, are primarily and essentially extremely rare forms of stenosis of the aorta. Stenosis of the aorta, as compared with that of the pulmonary artery, is rather rare, the relation being about that of one to four, and of extreme forms like those about to be presented I have been able to find a record of only three or four in the literature. Aortic stenoses are classified by Herxheimer (Schwalbe's Handbuch) as follows: (1) Those involving the conus up to the valves; (2) those occurring in the region of the ductus arteriosus; (3) general hypoplasia of the aorta.

These two cases illustrate extreme degrees of classes one and two respectively.

Case 1. This heart was taken from a well-developed and nourished male child aged five days, born of apparently healthy parents. On the afternoon of the fifth day, he became diffusely cyanotic, developed convulsions and died suddenly. Apart from the heart, the viscera were well developed and showed no evidence of disease other than passive congestion. The heart at first sight appeared to be a three-chambered organ, consisting of two auricles and one ventricle (the right), but on further dissection I found the following: (1) a large right auricle with normal entrance of the venæ cavæ, patent coronary sinus and foramen ovale; (2) a large right ventricle with thick walls and distended chamber occupying

two-thirds of the interior of the organ, normal tricuspid and pulmonary valves, large conus and main artery which after giving off the right and left pulmonary branches is continued as the ductus which arches downwards to form the descending aorta; (3) from about the middle of the arch of the ductus a branch about half its size is given off to the right and this in turn gives off the left subclavian, carotid, and innominate above while it sends a small branch, 1 to 2 mm. in diameter, downwards to the right of and behind the pulmonary artery where it terminates in the right and left coronary arteries with normal branching and distribution; (4) the left

FIG. 1. Drawing of heart in case 1. Right ventricle and pulmonary artery opened.

auricle receives the pulmonary veins normally. It is about one-third the size of the right. The foramen ovale is patent. The mitral valve is represented by a tense sheet of endocardium without chordæ tendineæ or papillary muscles. Beneath this is a small endocardial lined, blind pocket about 3 x 5 mm., representing the left ventricle from which there is no outlet.

This is a case of atresia of the whole left conus up to the aortic valves with resulting non-development and atrophy of the

left ventricle and of the ascending aorta, the only function of the latter being to supply the coronary arteries with blood received through the ductus arteriosus.

Case 2. This case also was that of a male child that died on the fifth day, having lived exactly one hundred and twenty hours. He was well developed and nourished, and the history of the parents, as far as could be ascertained, was negative. On the afternoon of the third day while nursing he became suddenly dyspnoëic, the respirations becoming very rapid and shallow. After this the whole surface of the body showed a dusky brown mottling. The temperature was 100.4. The urine showed albumin and a few pus cells. On the fourth day the dyspnoëa and cyanosis

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FIG. 2. Semi-diagrammatic drawing showing coronary arteries branching from the atrophic ascending aorta.

were more pronounced. The capillary circulation of the finger tips was good and recessive on inspiration. Systolic murmurs were heard over the whole cardiac area but were not transmitted to the axilla or vessels of the neck. In the right infrascapular region was an area of dulness with increased voice sounds. On the sixth day the child died and the body was sectioned. All the tissues showed passive congestion and considerable edema. The lungs showed atelectasis, congestion, edema and some patches of pneumonia. The description of the heart is as follows: (1) The right auricle is quite large with the openings of the cavæ and coronary sinus in normal position. The septum ovale (primum) is absent, leaving a large irregular opening between the two auricles. (2) The right ventricle has a large chamber and thick walls (nearly twice as large as the left). The tricuspid valve is defective, irregularly formed and has vegetations on

the cusps. The conus is large and points upwards to the right instead of to the left. There is a triangular-shaped opening about $10 \times 7 \times 7$ mm. in the bulbar region of the interventricular septum (Kieth's Bulbar Defect). The cusps of the pulmonary valve are covered with low vegetations. The pulmonary artery is large and lies slightly behind and well to the right of the aorta. After the right and left pulmonary branches are given off, the ductus arteriosus arches up and then turns downward to form the descending aorta. The only communication between the ductus and aorta is a small

FIG. 3. Drawing of heart in case 2, showing right ventricle and pulmonary artery open, patent interventricular septum, vegetations on valves, atresic isthmus.

fibrous thread, one mm. in diameter, extending between its outer surface and that of the left carotid, which represents the obliterated isthmic portion of the aorta. (3) The left auricle and ventricle are only about half the size of the right chambers, the ventricle being in front of and twisted around the left ventricle as the latter is twisted around it normally. The mitral valve is deformed by fibrous adhesions and vegetations. The aortic valve is normal. The aorta emerges to the left and in front of the pulmonary artery and terminates in the innominate, left carotid and left subclavian branches. In short the left heart supplies the upper, while the right supplies the lower part of the body.

This is an extreme form of the second class of aortic stenoses,

namely, stenosis—in this case atresia—in the isthmus or ductus region. There are two well-recognized forms of constriction in this region: (1) the fetal type, in which the stenosis is so great that the ductus must remain patent in order that life may continue; (2) the adult type, in which the constriction is not so great as to necessitate continued patency of the ductus. In this case it usually closes after birth. Later in life the constriction increases and necessitates the development of anastomoses between branches arising above and below the stenosis (internal mammaries, epigastric, scapular, intercostals, etc.).

Discussion:

DR. NORRIS: I should like to ask in the first case of congenital heart disease whether there was any transposition of viscera or any other anomaly.

DR. FRASER: No. There were no other anomalies in either case. They were both well-developed children.

TYPHOID LESIONS OF THE KIDNEY

ALEXANDER FRASER, M.D.

The lesion of the kidney usually found in typhoid fever consists of the degenerative changes common to all acute infections, or occasionally of embolic abscesses due to secondary infection. As far as I am aware, the specific typhoid lesion has not been described. Osler in his text-book on medicine mentions, without giving references, that Rayer, Wagner and others had encountered "small lymphomata which later may go on to suppuration," but evidently neither he nor they interpreted these as a specific reaction to the typhoid bacillus. Mallory, to whom I had shown sections of the cases about to be described, told me that he had seen an occasional small focus of endothelial leucocytic reaction, but never lesions so extensive or so typically developed as in this case.

The patient, a young sailor twenty-three years old at the time of his admission to St. Vincent's Hospital, had been ill eight days with a very

toxic acute infection. He had roseolæ, some of which were hemorrhagic, a well-marked leucopenia with relative lymphocytosis, and gave several positive Widal reactions. The urine contained numerous cells which were interpreted as pus cells, but which judging from the results of an examination of the urine found in the bladder at autopsy I am satisfied were mononuclear phagocytes with ingested lymphocytes. The autopsy, which was performed about fourteen days from the onset of the first symptoms noticed, showed numerous typical typhoid lesions, mostly "cribriform" ulcers in the

FIG. 1. Low power microphotograph showing typhoid lesion with central necrosis.

ileum and caecum together with greatly enlarged, congested and occasionally hemorrhagic mesenteric lymph nodes. Microscopic examination confirmed the presence of true typhoid lesions in the intestine, lymph nodes spleen and bone marrow, but not in the liver. The kidneys presented a remarkable picture. They were both large and diffusely congested with numerous yellowish-white, elevated, rounded or oval areas with deep red borders scattered over the whole surface. Section showed these spots penetrating the whole of

FIG. 2. High power microphotograph showing mononuclear phagocytes with ingested lymphocytes.

the parenchyma of both organs, presenting in the pyramids as long yellow streaks, extending over the pelvis and mucosal surface of the ureters and spreading out over the mucosa of the bladder. To the naked eye the picture suggested staphylococcus embolic abscesses, but microscopic examination showed no polymorphonuclear leucocytes. The lesions consist of round, or elongated oval collections of large mononuclear phagocytes with extensive central necrosis (Fig. 1.) The well-preserved peripheral parts consist of a fair number of lymphocytes but mostly of large phagocytes containing lymphocytes and occasionally red blood cells in their cytoplasm, many of them showing ten to fifteen cells at a single focus (Fig. 2).

Such cases must be exceedingly rare or they have been overlooked in the routine examination of typhoid patients and interpreted as cases of secondary embolic abscesses. Histological examination of six museum specimens labeled "embolic nephritis" reveals one case exactly like this. So, too, examination of large numbers of sections from kidneys in typhoid fever, showing nothing macroscopically, convinces me that small isolated foci of true typhoid reaction are not at all infrequent. It is not improbable, too, that more careful microscopic examination of the urine in typhoid would show that not infrequently the "pus" cells found are mononuclears with ingested lymphocytes. A quick way of settling the question would be the use of the oxydase reaction.

HYPERPLASIA OF THE PARATHYROID GLANDS IN RICKETS

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Of late years considerable attention has been directed to structural changes in the parathyroid glands associated with diseases in which there is a disturbance of calcium metabolism.

Erdheim¹ had found in the rickets of rats a hyperplasia and hypertrophy of the parathyroid glands proportional to the intensity and the duration of rickets in the animals. He found

also more numerous mitoses in the glands from rachitic than in those from normal animals. Although the reasons for these parathyroid changes are still to be explained, Erdheim regarded them as secondary to the rachitic lesions and not as the cause of them. In the parathyroids from human cases Erdheim was unable to differentiate histologically glands from rachitic and non-rachitic children.

Ritter² has recently studied the parathyroids from ten rachitic and fifteen non-rachitic children. None of his non-rachitic cases, however, fell within the usual age limits for the occurrence of rickets in children. He found that while in non-rachitic children in the first year the parathyroids consisted predominantly of clear cells belonging to the so-called Type I, in rachitic children they consisted almost entirely of dark smaller cells belonging to Type II, usually showed a marked increase in fibrous tissue, and marked hyperemia and edema. He also concluded from his study that no influence of the general state of nutrition of the child upon the histology of the parathyroid could be recognized.

The present study was made on the parathyroid glands of fourteen rachitic and eighteen non-rachitic children—routine autopsy material from the Nursery and Child's Hospital. Twenty-two separate glands were studied in the rachitic, nineteen in the non-rachitic cases.

In order to gain a general idea of the comparative size of glands from rachitic and non-rachitic infants, the sections were outlined at a constant magnification by the use of a projection apparatus. Allowing even for the gross inaccuracies of a method depending on the size of sections not known to be through the plane of greatest diameter of the gland, the area of the sections from the rachitic cases in almost every instance surpasses, and often greatly surpasses, that of the sections from the non-rachitic. Translated into volume, this certainly indicates a great excess of glandular tissue in the rachitic cases.

Our next problem then was to determine whether this increase in size were due to increase in the size of the individual cells, or to the multiplication of cells, or to some other factor. Choosing

five glands from the rachitic and five from the non-rachitic series, from children of approximately the same age, careful measurements were made with the micrometer eye-piece of fifty cells and nuclei from each gland. The cells were chosen at random from all portions of the glands, only making sure to choose those as symmetrical in shape as possible. The results are shown in the table:

| | Case No. | Age in Months | Nutrition | Cell Diameter in μ | Nucleus Diameter in μ |
|-------------------|----------|---------------|-----------|------------------------|---------------------------|
| Non-rachitic..... | 289 | 3 | Poor | 7.76 | 5.21 |
| | 299 | 6 | Good | 7.30 | 5.87 |
| | 325 | 9½ | Fair | 10.16 | 5.13 |
| | 329 | 9½ | Good | 10.20 | 5.83 |
| | 321(II) | 12 | Fair | 7.14 | 5.39 |
| Rachitic..... | 361 | 5 | Emaciated | 10.09 | 5.24 |
| | 333(II) | 8 | Good | 8.41 | 5.26 |
| | 334 | 9 | Emaciated | 7.51 | 5.10 |
| | 375 | 10 | Good | 9.30 | 4.92 |
| | 335 | 12 | Good | 10.31 | 6.23 |

It will be seen that there was found no constant difference in the size of either cells or nuclei in rachitic as contrasted with non-rachitic cases. Neither was there shown any constant relation of the size of cell or nucleus to the nutritional state of the child. Since the histologic study showed no increase in connective tissue, no edema and no difference in vascularity or congestion, we felt justified in concluding that the increase in size of the glands in rachitic cases is due to multiplication of cells.

A brief résumé of the histology of the parathyroid gland is as follows: There are three general types of cell arrangement—in compact masses, as cords of cells separated by blood vessels and connective tissue septa, and a less frequent form showing a lobular structure. There are also three types of cell found: I, clear, vegetable-like cells with unstained cytoplasm, large vesicular nuclei and clear cell outlines; II, rose-red cells with finely granular cytoplasm, small dark nuclei and indefinite cell outlines; III, Welch's oxyphile cells, which last are rarely found before the tenth year.

Comparative histologic study of the twenty-two glands from rachitic and nineteen from non-rachitic cases revealed no constant differentiating features. There was an increase in connective tissue in the glands in only one rachitic case, and this increase was only slight. There was no greater vascularity or congestion in rachitic than in non-rachitic cases, and no evidences of edema were found.

In all our sections, the clear cell belonging to Type I predominated markedly, and as constantly in rachitic as in non-rachitic cases. The other cells present belonged to Type II and showed no constant arrangement with regard to blood vessels. No mitoses were found; this, however, could easily be due to lateness of fixation.

Our conclusions from this study, then, are:

1. That there is a very definite increase in the size of the parathyroid gland in cases of human rickets, and that this increase in size is due to multiplication of cells, not to an hypertrophy of individual cells or increase in supporting structures.
2. That the parathyroid glands in children within the first eighteen months of life consist predominantly of clear cells belonging to Type I.
3. That in human rickets there is no constant or characteristic change in the cell type, and the clear cells still remain markedly predominant.
4. That in our cases there was no increase in supporting tissues in the parathyroid gland in rickets, and no increase in vascular supply, or evidence of congestion not found equally in non-rachitic cases.
5. That the state of nutrition of the child had no bearing on the size either of the gland as a whole or of the individual elements.

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Discussion:

DR. JOBLING: Definite conclusions cannot be drawn from this study by Drs. Minor and Pappenheimer, as the glands were not weighed and measured at the time they were removed, but the results are very suggestive.

DR. PAPPENHEIMER: There is an apparent paradox in the relation of the parathyroids to calcification, which has not been explained. It is generally known from the work of Erdheim and Toyofuko that complete destruction of the parathyroid in rats is followed by a failure of the dentine to take up calcium and also by a lack of calcium deposition in the callus of experimentally produced fractures. Identical changes, as regards the failure of calcium deposition, occur in rickets, but associated with a hyperplasia of the parathyroid. One can of course theorize about the explanation of this seeming discrepancy, but there is as yet no real explanation.

PRIMARY BONE TUMORS

THEIR CLASSIFICATION WITH SPECIAL REFERENCE TO BENIGN GIANT-CELL TUMOR

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For a number of years I have noted a considerable confusion and lack of clear thought among surgeons and pathologists as regards the diagnosis, treatment and prognosis of the primary tumors of the long pipe bones belonging to the so-called sarcoma group.

It is rather unfortunate that even at the present time many able and even noted surgeons are extensively sacrificing limbs for tumors which have been known to be distinctly benign in character.

It is for this reason that I will attempt to summarize some of my experiences encountered in this type of tumors. I have tried to do this in as practical a way as possible, consequently much scientific data will obviously escape recognition in this discussion.

The primary mesenchymal tumors of bone may be roughly classified as follows:

TABLE I

CLASSIFICATION OF PRIMARY TUMORS OF BONE

Primary Mesenchymal Tumors of Bone

FIBROBLASTOMA (fibroblast).

Benign: Fibroma, and border-line fibrosarcoma (unusual).*Malignant:* Fibrosarcoma (see osteogenic sarcoma).

MYXOBLASTOMA (myxoblast).

Benign: Myxoma, myxofibroma, myxolipoma and myxochondroma.*Malignant:* Myxosarcoma, myxochondrosarcoma and osteomyxochondroma.

CHONDROBLASTOMA (chondroblast).

Benign: Chondroma, ecchondrosis, chondromyxoma and osteochondroma. Multiple congenital enchondromata.*Malignant:* Chondrosarcoma, osteochondrosarcoma, etc.

OSTEOBLASTOMA (osteoblast).

Benign: Osteoma, osteophytes, exostosis, endostosis, osteofibroma, etc.*Malignant:* Osteogenic sarcoma.

ENDOTHELIOBLASTOMA (blood-vessel endothelioblast).

Benign: None.*Malignant:* Endothelial myelomas and multiple hemangioendothelioma.

MYELOMA (type cell unknown).

Benign: None.*Malignant:* Multiple myeloma (Kahler's disease).

BENIGN GIANT CELL TUMOR.

Benign: Single and multiple forms of disease (see osteitis fibrosa).*Malignant:* None.

If we examine Table I, it will be readily seen that most of the tumors group themselves into benign and malignant forms. Most of the benign forms, though not all of them, can as a rule be easily diagnosed by their history, location, age incidence, clinical appearance and X-ray examination, and therefore offer little confusion either to surgeons or pathologists.

Furthermore, the malignant forms, if studied more in detail, will dwindle down to a few important types. For example, fibrosarcoma would be a rare bone tumor if we interpret tumors belonging to this class as a fibrocellular variety of osteogenic sarcoma. In a like manner, myxosarcoma, myxochondrosarcoma, chondrosarcoma, etc., while they do occur as pure forms which metastasize, are nevertheless most often encountered as metaplastic areas in osteogenic sarcoma.

The confusing primary tumors of the long pipe bones, when

a question of malignancy arises, usually exclude all but the following: osteogenic sarcoma, endothelioma, multiple myeloma and benign giant-cell tumor.

My experience has been that it is impossible, especially in central varieties of these tumors, to diagnose many of them from their age incidence, location of tumor or X-ray examination, but that an exploratory incision with histological examination of the tissue removed is necessary.

OSTEOGENIC SARCOMA

Of the many anatomical varieties of this tumor described in the literature, for teaching purposes I have adopted the simple classification of Ewing as the best, namely, fibrocellular and chiefly periosteal; telangiectatic, soft and richly permeated with blood-vessels and sinuses (bone aneurysm), involving marrow, shaft and periosteum; and sclerosing, a very hard osteoblastic growth, involving marrow, shaft and periosteum, and to a slight extent less malignant than the other two forms.

It has been found that practically all these growths sooner or later involve the periosteum, making a classification as periosteal sarcoma justifiable in a large majority of the cases. A central sarcoma without involvement of the periosteum I have never seen, and this is interesting, since Bloodgood has recently stated, "I would welcome an opportunity to study a solid central sarcoma in which there is no periosteal growth."

The important facts in osteogenic sarcoma are summarized in Table II.

TABLE II

SUMMARY OF IMPORTANT DATA IN OSTEOGENIC SARCOMA
PATHOLOGY:

| <i>Anatomical varieties</i> | <i>Location</i> |
|-----------------------------|------------------------------|
| 1. Fibrocellular..... | Chiefly periosteal |
| 2. Telangiectatic..... | Marrow, shaft and periosteum |
| 3. Sclerosing..... | Marrow, shaft and periosteum |
| 4. Capsular | |
| 5. Parosteal | |

HISTOLOGY:

Type cell: spindle, round and tumor giant cells.

Production of new bone.

Hyperchromatic nuclei and tumor mitoses.

CAUSE OF DEATH:

Early lung metastases.

AGE INCIDENCE:

Fifteen to seventy years. Cases few before fifteenth or twentieth year.

TREATMENT:

Radical Operation and treatment of any kind almost hopeless. Blood-good's series showing less than 4 per cent. cures after radical operation and early diagnosis.

Radium supposed to be of little or no benefit (see Ewing's discussion).

ENDOTHELIOMA OF BONE

True primary endothelioma of bone has always been questioned by many pathologists, because of the close histological resemblance of the growth to metastasizing adrenal tumors, tumors of the thyroid, prostate, etc.

I believe that it does occur rather frequently as a single tumor. Rare multiple forms have been described, notably a case of multiple hæmangioendothelioma reported by Symmers, which clinically simulated multiple myeloma.

The importance of this type of bone tumor has recently been emphasized by Ewing, who a few months ago presented to this Society several cases of, I believe, undoubted primary endothelioma of bone, the cases being clear cut enough to form a distinct clinical and pathological entity in bone tumors. This remarkable contribution to the pathology of bone tumors, sharply identifying a type of tumor frequently submerged under the name of round-cell sarcoma, and often mistaken by pathologists for osteogenic sarcoma, is of especial importance, since the malignancy of this tumor is very much less than that of osteogenic sarcoma, persistent X-ray or radium treatment checking and apparently curing the lesion.

TABLE III

SUMMARY OF SALIENT POINTS IN ENDOTHELIOMA OF BONE

PATHOLOGY:

Anatomical varieties

1. *Single tumor:*

(a) Circumscribed, large bulky growths, arising in marrow or endosteum and early perforating shaft and developing externally.

(b) Smaller growths, many occurring in middle of shaft, and submerged in the diagnosis of round-cell sarcoma, periosteal sarcoma, etc. (Ewing's endothelial myeloma).

2. *Multiple Tumors:*

(a) Multiple hemangioendothelioma (Symmers), clinically resembling multiple myeloma.

HISTOLOGY:

1. *Single Tumor:*

Type cell is a round or oval-shaped cell with clear cytoplasm and vesicular nucleus. Usually arranged in alveolar formation with little or no intercellular substance. Some portions of the tumor showing origin from blood-vessel endothelium. There is absence of new bone formation, but bone absorption is common.

2. *Multiple Tumors:*

In Symmers's case the histological picture of hemangioendothelioma or angioma was very evident.

CLINICAL COURSE:

The single tumors are not nearly so malignant as osteogenic sarcoma and perhaps amenable to X-ray and radium treatment. Ewing states that tumors rapidly melt under radium but recur unless treatment is persistent.

MULTIPLE MYELOMA

This is most easily diagnosed by the X-ray examination showing multiple bone tumors, which demonstrates the importance of raying the skeleton in many bone tumor cases. The X-rays being distinguished from multiple metastasizing carcinoma by its predilection for bones with red-marrow and the absence of a moth-eaten appearance.

In a tumor in which the type cell is unknown, and has been described as a myelocyte, lymphocyte, plasmocyte or erythroblast, it is quite possible that with so great a variation in histological structure the explanation may be that we are dealing with an undifferentiated metrocyte, somewhat similar to the explanation suggested by Symmers in the disease "Leukanæmia" (a combination of myelogenous leukæmia and pernicious anæmia).

Multiple myeloma is a rare disease occurring in individuals over thirty-five years of age, oftenest in men, and pursuing a

rapidly fatal course. It is characterized by foci of growth arising in different parts of the marrow system at approximately the same time involving bones with red-marrow, as vertebræ, sternum, ribs, skull, scapulæ and ilium. Spontaneous fractures are common. Bence-Jones albumose is frequently found in the urine.

It occurs in two anatomical varieties, the ordinary form or Kahler's disease in which the lesions are confined to the bones, and a very rare or extra-medullary form in which the lesions may be present in other tissues.

Histologically the type cell has been identified as either unknown, an adult or embryonal myelocyte, a lymphocyte, a plasma cell, or in rare instances as an erythroblast.

Treatment in this disease is of no avail, except mechanical to relieve pressure symptoms.

BENIGN GIANT-CELL TUMOR

Benign giant-cell tumor, medullary giant-cell sarcoma, giant-cell sarcoma of the epulis type, medullary giant-cell tumor, chronic non-suppurative hemorrhagic osteomyelitis (Barrie), etc., has been recognized for many years by a few surgeons and pathologists as essentially a benign lesion of bone. This fact, however, is unfortunately not appreciated by most surgeons, in spite of all the literature written on the subject.

The tumors usually occur in the ends of the long bones, especially the upper end of the tibia. The majority occur in young people. A definite history of trauma is often obtained and seems to be an important etiological factor in the single lesions. Their growth is slow and duration of disease long. They recur after incomplete removal, *in loco*, but I have never seen one metastasize to distant parts.

X-ray examination shows an expansive, abrupt and circumscribed growth with preservation of the bony shell. Distention may be great.

In gross appearance the tumor is usually confined within the periosteum, definitely circumscribed, not infiltrating, and is easily removed from its bony shell. It is distinctly vascular, simulates

young granulation tissue, is friable, soft, oozes and resembles red-currant jelly or fresh-cut liver.

Histological examination shows a stroma like young granulation tissue, ranging from very cellular, often hemorrhagic, areas to older, non-cellular portions in which the fibroblasts are arranged in whorls and resemble slightly spindle-cell sarcoma. Active mitoses and hyperchromatic nuclei are, however, not present. Giant cells of the foreign body endothelial type with glassy cytoplasm and many (25 to 80) vesicular nuclei are numerous, often forming the predominant picture.

It has been my good fortune to have had under observation with Dr. F. R. Haussling, attending surgeon to the City Hospital, a case of benign giant-cell tumor of the lower end of the tibia for a period of ten years, during which time the lesion has been curetted several times. During this time we have noticed, both from the X-ray examinations, the character of lesion at operation and the histological examination of the tissue, that the lesion has been changing in character from an original solid benign giant-cell tumor to an extensive, localized fibro-cystic disease of the tibia. The lower end of the tibia at the present time shows a very large multilocular cyst of the bone with an old fibrous wall containing only a few giant cells.

I have also had the opportunity of following with Dr. Haussling a very remarkable case of multiple giant-cell tumors for a period of six years. This case I reported before this Society in 1915. At the present time only four well-marked cases of this disease have appeared in American literature.

For several years the tumors in this case which were located in the right superior maxilla, both fibulae, both clavicles, femurs and ribs were expansive, more or less solid tumors chiefly in the myeloid part of the bones and well confined within their bony shells. They showed the typical histological picture of benign giant-cell tumor.

During the last two years, even in lesions which had not been curetted, these tumors have been becoming cystic along with extensive fibrocystic disease of the surrounding bone. The gross

appearance of one of the lesions at last operation was one of multiple cysts with fibrous walls, showing histologically dense fibroblastic tissue with scant foreign body giant cells.

I do not believe that any single lesion has been under such a long observation, since the tumor is either cured by surgical curettement, etc., or the limb sacrificed by some ill-informed surgeon.

The multiple lesions in their extreme form are so rare that it is doubtful if any case has been observed over such a period of time. The changing in the character of the gross appearance and microscopic picture of the lesions in both the single and multiple case during this time of observation is, in my opinion, extremely interesting.

From my observations in these two cases I am of the opinion that so-called benign giant-cell tumor is entirely an inflammatory process in the nature of exuberant granulation tissue, located mainly in the myeloid part of the bone, formed as an attempt to repair previous bone destruction, due to trauma in the single lesions and in the multiple ones to some unknown cause. I believe the disease is one phase or rather an exaggerated phase of *osteitis fibrosa cystica*.

It is interesting to note that very similar growths are occasionally seen in the tendon sheaths which have microscopic pictures closely resembling these giant-cell tumors of bone, namely, the so-called benign xanthic extra-periosteal tumors of the extremities.

My conception of so-called *osteitis fibrosa cystica* may be roughly summarized in Table IV.

TABLE IV

SUMMARY OF IMPORTANT DATA IN OSTEITIS FIBROSA CYSTICA

NAME OF DISEASE: In my opinion no good, permanent name has been suggested so far. Metaplastic osteomalacia is worth considering.

PATHOLOGY:

Anatomical varieties

1. *Localized lesions* (localized osteitis fibrosa cystica).
2. *Generalized lesions* (generalized osteitis fibrosa cystica of von Recklinghausen).

Location

Practically always in diaphysis and never invades epiphysis. Slow growth and moves up diaphysis. Most common in proximal end of shaft.

Etiology

In single lesion trauma seems to be an important exciting factor. In generalized type of disease the cause is unknown, may be bacterial, nutritional or endocrinal. Usually appears before thirtieth year.

Sequence of Lesions

1. Destruction and absorption of bone (usually medullary in cancellous bone).
2. Granulation tissue formed in effort of repair; producing picture of young granulation tissue with hemorrhage, bone absorption and numerous foreign body endothelial giant cells.
3. Replacement by a less cellular fibroblastic tissue, a medullary fibrosis; producing a picture simulating spindle-cell sarcoma.
4. The lesion at this stage may progress in any of the following ways:
 - (a) Subside, due to softening of fibrous tissue, with formation of single or multiple bone cysts lined by a fibrous wall, the cyst fluid eventually becoming serous and often clear.
 - (b) Progress as a solid giant-cell tumor with or without cyst formation and finally heal or become bone cyst.
 - (c) Progress rapidly as a benign solid giant-cell tumor of local clinical malignancy with considerable destruction of bone.

TREATMENT: Radium or surgical curetting with crushing of diseased wall. The success of surgical treatment in our opinion has been due chiefly to *closure without drainage*, thus avoiding sepsis.

SUMMARY OF CASES REPORTED

CASE I. Single, solid benign giant-cell tumor of lower end of tibia, changing in a period of ten years into a single multilocular bone cyst.

A. L. Male. Italian. Present age thirty-eight years. Barber.

Family History: Negative.

Past History: Chancre when eighteen years of age.

Present History:

1907. Twisted right ankle while playing ball.

In plaster 3 weeks.

Syphilitic treatment for 3 months.

Plaster for 2 months.

Lower end of tibia curetted and discharged cured.

1908. Swelling and pain has returned.

Lower end of tibia curetted, diagnosis osteomyelitis.

Sinus persisted.

1910. Fell and injured ankle.

Admitted to City Hospital.

Lower end of tibia curetted and diagnosis of solid benign giant-cell tumor made.

1911. Tibia curetted 4 times for recurrence.

1915. Tibia curetted for recurrence. The original tumor is no longer composed of granulation tissue, but consists of several cystic cavities filled with serous fluid.

1921. Patient in good physical condition. Has been able to work as barber all this time. X-ray examination shows a multilocular communicating cyst involving lower third of tibia.

CASE 2. Multiple, solid, expansive benign giant-cell tumors, changing in a period of six years into generalized fibrocystic disease of long bones.

T. K. Female. White. Present age thirty-one years. Married.

Family History: Negative.

Past History: Venereal diseases denied. Four normal births, one miscarriage.

1914. Noticed lump in inner angle of right eye.

Fell and fractured right femur above knee, which united with fair result.

Noticed tumor mass on anterior surface of left tibia.

Admitted to hospital complaining of weakness and pain in bones.

1st operation: tibial tumor curetted, microscopical diagnosis benign giant-cell tumor.

2d operation: tumors in maxilla, both fibulae, both clavicles and rib curetted. Gross appearance of tumors that of pale granulation tissue, microscopical diagnosis benign giant-cell tumor.

3d operation: right elbow curetted.

1916. *4th operation:* left femur curetted.

1917. *5th operation:* right tibia curetted.

6th operation: clavicle curetted.

1919. *7th operation:* both tibiae and left clavicle curetted.

8th operation: left femur curetted.

9th operation: finger curetted.

1920. *10th operation:* left femur curetted.

11th operation: left femur curetted.

1921. *12th operation:* left tibia curetted.

At all operations the wound was closed by primary suture without drains, this we regarded as a very important factor in preventing sepsis. The present physical condition of the patient is fair considering her long stay in hospital. She has a moderate secondary anæmia. Her blood chemistry is normal for nitrogenous waste retention, her calcium metabolism, however, has never been determined. The tumor masses in the last few years are distinctly cystic at operation and histological examination shows scant or no giant-cells present but old, dense fibroblastic cyst walls. The indication for operation has been pain. Many of the lesions have disappeared without surgical treatment but the surrounding bone shows extensive fibrocystic disease.

Of the American literature on bone tumors, especially giant-cell tumors, I have been greatly helped in my observations by the numerous writings of Bloodgood, Ewing, Barrie, Symmers and Meyerding.

Discussion:

DR. MOSCHCOWITZ: In twenty years' experience I have never seen a patient with a giant-cell sarcoma of the bone come to autopsy. I should like to ask those here if they have had the same experience.

DR. SYMMERS: What part of the bone do you mean?

DR. MOSCHCOWITZ: Any giant-cell sarcoma.

DR. EWING: I think Dr. Martland has given us a great deal of valuable information. I wish he could find time to carry it around to the places where it would do most good. Although the general statements which he mentioned have been known since 1852, the information needs to be spread broadcast in this country. At a recent meeting in this city of prominent surgeons about thirty were present, who were presented with evidence such as has been given to-night of a giant-celled sarcoma in the tibia with all the features and histology described, and they were asked to state what they would do. Twelve of the thirty would amputate. I think this is a deplorable state of affairs when the information is as clear as it is of the benign nature of this disease. The difficulty is not with these characteristic growths in which a large portion of the tumor is made up of giant cells, but in the variants of this disease. I have found quite a few tumors which are in all respects like those described, but in which the giant cells are scattered and the remaining tumor tissue is quite cellular and verging toward the ordinary malignant looking spindle-cell sarcoma. I am unable to come to a conclusion as to whether there are two diseases here which you cannot distinguish histologically and clinically, or by the X-ray, or whether this ordinary simple benign giant-cell tumor may in different cases become a clinically malignant, possibly metastasizing tumor. I am unable to decide what its relations are to the malignant cases of true osteogenic sarcoma. In cutting the capsules of these tumors I find varying degrees of bone formation and bone absorption, and if one sees only small sections, it is very difficult to distinguish the process from malignant osteogenic sarcoma, so I think it is better not to cut into these tumors and attempt to make a diagnosis on a small piece of tissue. One ought to have all the data in the case, including the X-ray. I have been looking for many years for an undoubted case of giant-cell sarcoma of the bone of the epulis type which had killed with metastases in the lungs. I have been unable to find such a case.

In regard to the treatment of these cases, which is really what the pathologist has to decide, my position is that none of these tumors should be cut into. You may not get a diagnosis. That so often happens in my experience that I prefer to rest the diagnosis on the clinical history, the age of the patient, the X-ray findings, and the general physical condition of

the patient and the tumor. I agree with Dr. Martland that you cannot make a positive diagnosis in all these cases, but an incision does not always do it. I know many cases that have lost their limbs, and several that have lost their lives, from infection from bone cysts after exploratory incision and curettage. Many of them do badly, and Dr. Martland's patient is very fortunate indeed to have escaped infection in so many operations. Another reason for reaching this decision is that the benign tumors of this sort respond very well to treatment by physical agents, X-ray and radium. So also do the myelomas. In the malignant osteogenic sarcoma no method of treatment is satisfactory or successful, yet prolonged X-ray and radium treatment of osteogenic sarcomas in at least two cases has caused a complete disappearance of the local tumors, and the patients have remained well for three and a half and four and a half years, respectively, so that I would like to see what thorough X-ray treatment would do with the malignant osteogenic sarcomas. It is however difficult to get an opportunity to carry this out, for the patient will sooner or later fall into the hands of some surgeon who will cut the leg off. I have not been able to get a fair test of these tumors, but I am optimistic enough to say that if the limb could be immobilized and thorough X-ray or radium treatment be given over long periods the result might very likely be better in a series of cases than it is at present with amputation.

DR. MARTLAND: In reference to Dr. Moschcowitz's question, I do not believe that benign giant-cell sarcoma as I have described it ever does metastasize. I know there are a few cases on record in which it is claimed that the stroma has undergone so-called sarcomatous proliferation, but this has been very rare in giant-cell tumors, and I think those tumors which have metastasized have been the so-called periosteal or osteogenic sarcomas, in which you get a number of foreign-body giant cells, but you also get true tumor giant cells.

I agree with Dr. Ewing that some of the most eminent surgeons, who have had the best experience in bone sarcoma, seem to have no idea at all of what they are dealing with pathologically, and it is unfortunate that in the large cities we see extensive sacrifices of limbs which are absolutely unwarranted.

PRIMARY SPINDLE CELL SARCOMA OF THE LIVER ASSOCIATED WITH CIRRHOSIS

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The reported cases of primary sarcoma of the liver have been collated by different authors, the latest collection being that of

Marx in 1904—57 cases. Marx analyzed many of these cases only to condemn them. He accepts the majority as sarcomatous, but thinks that the evidence of their origin in the liver is unsatisfactory. Some cases were attended by smaller tumors in other organs, such as the adrenal or the periosteum of the vertebræ that Marx considers may have represented primary growths. Others were incompletely investigated post mortem or lacked autopsies altogether, the diagnosis being based on operative findings. Marx concludes, however, that when all these cases are excluded there remain a considerable number of undoubted primary sarcomata of the liver. Others have still further reduced the number of unchallenged cases by questioning the sarcomatous nature of many of the growths. Ewing emphasizes the danger of classifying growths with an alveolar structure as of connective tissue origin, and points out the resemblance of some of the tumors reported as angiosarcomata to atypical carcinomata. The rarity of cases acceptable to all makes it a duty to report the following, in which the diagnosis of sarcoma appears to be unquestionable, and in which there is no reasonable doubt that the growth had its origin in the liver.

The patient was a laborer, aged forty-seven, born in this country. The family history was uncertain; he denied venereal disease and the use of alcohol and tobacco. He professed to have had no severe illnesses until fourteen months before his death, when he suffered from an acute abdominal attack with pain in the right upper quadrant. He did not know whether he was jaundiced at that time. A diagnosis of gall stones was made and at operation a fistula was made from the gall-bladder to the abdominal wall; this fistula remained open until death. He did not know whether gall stones were found. He returned to work and remained well until February, 1921, when his legs and scrotum commenced to swell. He was admitted to Bellevue Hospital on the service of Dr. Charles Nammack on February 16, 1921, and died eleven days later. During his stay in the hospital the patient was intensely jaundiced and moderately emaciated; mentally he was dull, not being aware of either the jaundice or the emaciation.

There were physical signs of pneumonia over both lower lobes. Examination of the heart was negative. In the epigastrium and right hypochondriac region there was felt a hard, nodular mass which corresponded in position to the liver and descended with inspiration. There was a ventral hernia at the site of a healed upper right rectus incision; at the upper end of the scar there was an open sinus discharging mucoid material. The scrotum

and both lower extremities were moderately edematous. During his stay in the hospital he had a temperature range of 98° to 100°, pulse 100 to 120, respiration 20 to 24. The leucocytic count was 10,200 with 84 per cent. polymorphonuclears; red cell count, 4,000,000. The urine was negative except for the presence of bile. A provisional diagnosis was made of carcinoma of the gall-bladder with extension to the liver. Pneumonia was apparently the immediate cause of death.

FIG. 1 Transverse section of liver through longest diameter.

Autopsy: The body was considerably emaciated, the abdomen slightly scaphoid. There was a moderate, soft, pitting edema of the lower extremities, scrotum and posterior body wall. The scleræ, skin and all the body tissues were intensely and uniformly icteric. There were large purpuric spots on the dorsum of both wrists and about the knees. The scar of the right rectus incision was recently healed at the upper extremity where the sinus had opened. The firm, nodular mass described could be felt two inches below in the xiphoid and just at the costal margin in the right mammary line.

The peritoneal cavity contained about 300 c.c. of thin, reddish-brown

fluid. The entire visceral and parietal peritoneum was studded with slightly elevated, rounded, grayish-white nodules, measuring 1 to 2 cm. in diameter. The omentum was adherent to the cæcum.

The liver was about normal in size but very firm and tough. The liver substance was broken up by trabeculae of white fibrous tissue distinctly seen on section, between which bulged out little nodules of brownish liver tissue. The surface was nodular, apparently from the same cause, the nodules varying in size from one to several millimeters. In the right lobe was a spherical mass, about 10 cm. in diameter, consisting of firm yellowish tissue mottled with areas of a salmon color, and everywhere streaked with



FIG. 2. High power photomicrograph of well-preserved portion of growth.

barely visible grayish fibers. There were some portions which were lighter yellow and very soft, but the major portion was as firm as the surrounding liver tissue. This mass was rather sharply circumscribed, but had no definite capsule. It projected slightly from the upper surface of the liver to form an irregular, white, firm protuberance over the major portion

of the right dome. Scattered throughout the liver were smaller nodules of similar tissue, some deeply imbedded, some on the surface. Those on the surface showed very slight umbilication and some showed central yellowish areas of softening. None of these masses was in close proximity to the gall-bladder, which was found in its normal site. The wall of the gall-bladder

FIG. 3. Low power photomicrograph of margin of growth, showing islands of liver cells cut off completely by the tumor cells. These cells are loaded with yellow granular pigment.

was thin and flexible, its mucosa apparently normal. From the fundus of the gall-bladder a sinus extended to the upper end of the abdominal scar, surrounded by dense white scar tissue. The duodenum and transverse colon were firmly adherent to the gall-bladder. They were opened before being dissected free and found to be normal. The œsophagus, stomach and small and large intestines were carefully explored, but no ulceration or tumor was found. Above the pancreas, from the head to the middle of the body, was a mass of discrete nodules of tumor tissue, suggesting replacement of lymph nodes. The pancreas was entirely separate from this mass and appeared

to be normal. This chain of nodules extended to the portal structures, where they surrounded and pressed on the portal vein and common bile duct.

There was a similar mass of tumor tissue, measuring 1 x 3 x 4 cm., lying in the anterior mediastinum, just above the diaphragm. Both pleural cavities were partially obliterated by adhesions; the right contained about 300 c.c. of thin, amber-colored fluid. The visceral pleura over both upper

FIG. 4. Metastatic nodule in suprapancreatic lymph node.

lobes was studded with nodules similar to those in the peritoneum. There were healed tuberculous scars in the pleura at both apices. Both lungs were congested and edematous throughout, and there was patchy consolidation in the left upper and lower and right lower lobes. There were no nodules of tumor tissue in the lungs. There was complete obliteration of the pericardial cavity by fibrous tissue.

The spleen was twice the normal size, soft and flabby, and, on section, raspberry-red in color with no focal changes.

The kidneys, adrenals, ureters, bladder, prostate, seminal vesicles, testes, epididymes, larynx, pharynx and thyroid were free from metastases and were essentially normal. No palpable enlargements were made out in the bony skeleton. Examination of the brain and spinal cord was not permitted.

Microscopic Examination: Microscopically, the well-preserved portions of the growth showed a uniform structure of large spindle cells lying in fasciculi, so that they were cut in all directions. They varied somewhat in size, but, in general, were large; the nuclei were oval, rich in chromatin and had no definite nucleoli. Mitotic figures were numerous. Occasionally there was a cell with two or three closely crowded nuclei, but these did not form a prominent feature of the growth. Blood vessels were rather scanty and they had no apparent influence on the structure or nutrition of the growth. There was no alveolar arrangement in any part of the tumor. Intercellular stroma was practically non-existent in some areas. In other places there was abundant hyaline transformation with a few scattered, elongated spindle cells. Other areas were frankly necrotic.

The liver tissue showed a high grade of cirrhosis, chiefly perilobular in type. There were wide bands of fibrous connective tissue with rich lymphocytic infiltration surrounding individual lobules or groups of lobules. In some places the connective tissue had grown between the cell cords. The liver cells toward the periphery of the lobules were loaded with pigment in yellowish-brown granules and the intercellular bile capillaries were distended with bile.

The tumor encroached directly on the liver tissue, without the intervention of a capsule, and tumor cells were seen growing into the liver lobules, enclosing finally small groups of liver cells or even individual ones loaded with granular pigment. There were numerous lymphocytes scattered through the growth, particularly in close proximity to the portal spaces.

The suprapancreatic nodes showed a pure spindle-cell growth with no necrosis or areas of hyalinization.

Of the tumors found, that in the liver clearly should rank as primary, and those in the lymph nodes, anterior mediastinum, pleura and peritoneum as metastatic.

Pure spindle-cell sarcomata of the liver were found only twice in a review of the literature, but many tumors were classed as spindle- and giant-cell, or spindle- and round-cell. The association with cirrhosis is interesting. Rolleston and Trevor collected seven cases, including one of their own, only one of which was a pure spindle-cell growth. In this the author found it impossible to say whether or not the cirrhosis antedated the tumor. In our case the cirrhosis is uniform throughout the organ and is of an advanced grade. In many of the nodules tumor cells are seen

growing in the inflammatory tissue in the portal spaces, so that the possibility is suggested of a multiple origin of the growth secondary to the cirrhosis.

Addenda: Acting on a suggestion made during the discussion, preparations of the liver have been stained by the Levaditi method for spirochætes and by carbol-fuchsin for tubercle bacilli, but no organisms have been found.

The following brief notes of two cases resembling ours quite closely are appended:

1. From Arnold, In *Ziegler's Beitrage*, 1890, viii, 123. A man, fifty-three years old, for six months before his death had increasing jaundice, ascites and edema of the feet. He was in the hospital for one month. A hard nodular mass was felt in the epigastrium. Paracentesis was done twice, removing blood-tinged fluid. At autopsy, he presented intense jaundice and moderate ascites (the abdomen contained six liters of bloody fluid). There were pea-sized nodules throughout the omentum and mesentery, a few in the serosa of the intestine and a few in the pleura and bronchial nodes. The liver was much enlarged, coarsely granular and icteric. There was much interlobular connective tissue, sometimes enclosing several lobules, more marked near the tumor. In the right lobe was a tumor measuring 13 x 10 cm. and reaching the capsule; there were several smaller tumors in the vicinity and a beet-sized nodule at the base of the pericardium. Microscopically, the growth showed round, angular and spindle-shaped cells and a few giant cells. They grew around the blood vessels and seemed to spring from the adventitia. Arnold felt that the histogenesis was not certain, but that the sarcomatous nature of the tumor was undoubted.

2. From W. W. Ford, *Amer. Jour. Med. Sc.*, 1900, p. 413. A man, aged 59, with a markedly alcoholic history, died as a result of cerebral thrombosis. His abdomen had been increasing in size for some time. At autopsy, he presented no jaundice. The abdomen contained 4,000 c.c. of clear yellow ascitic fluid. The mesentery and omentum were filled with small nodules the size of a pea, white or reddish; similar nodules were scattered over the peritoneal surface of the abdominal muscles and diaphragm. The liver was small and showed an advanced grade of cirrhosis, principally intra-lobular. There was a tumor measuring 5 x 8 cm. in the right lobe. The center was soft, white and friable, the peripheral portions firm and grayish white. Microscopically, it consisted of round and spindle cells with central necrosis. The metastases were of the same structure with many blood vessels.

Discussion:

DR. EWING: I should like to express my great interest in this case. I have never seen anything like it. I do not feel that there is any definite

ground on which one can successfully attack the diagnosis. It is unique in my experience, and as far as I know, there is nothing exactly like it in the literature.

DR. NORRIS: I have not had a very good look at the section. It was under low power, and I would not want to say anything about it. The question of these sarcomas of the liver is however occasionally very difficult to decide. I remember I reported the case of a woman before this Society six or seven years ago, in which Dr. Hermann M. Biggs made the clinical diagnosis of primary sarcoma of the liver. It was a very large liver, weighing two or three pounds, and at autopsy there was found an epithelioma just above the cardia of the esophagus. The sections of that tumor are strikingly like a sarcoma and I presented it, and received considerable credit and discredit for bringing it to the Society just for diagnosis. I suppose in that case, where there was a distinct primary tumor at the lower end of the esophagus, the only fair conclusion was to call it a carcinoma, but that tumor as I recollect was very vascular and had a tendency toward alveolar formation and distinct large spindle cells. This tumor to-night evidently has small spindle cells, and apparently has no resemblance to a carcinoma or an epithelioma. It seems to me with the hasty examination I have been able to give it that the diagnosis of primary sarcoma is the correct one.

DR. EWING: Did you consider the possibility that this might be a peculiar granuloma? There are a great many lymphocytes all through the tissue. The general behavior of this tumor seems to me not that of a sarcoma. The tumor is not very bulky. It seems to replace the liver rather than to cause a great increase in the bulk of the tissue. It invades the lymph nodes, which sarcomata do not do, as a rule, and it is not in the lungs. There is very extensive necrosis in the tumor, which suggests doubt as to its nature. I am not convinced that this is properly to be classed as a simple sarcoma. What is sarcoma anyway?

DR. NORRIS: May I have another word? Although I hesitate to mention it, in all these rare tumors of the liver one must always think of melanoma, though it seems extraordinary to bring it up in reference to this case. Melanomas are so variable that a primary tumor might have been neglected or overlooked. I see no reason for thinking it is a melanoma, but I remember one case of a woman who had an eyeball tumor about six years ago. She had a melanoma, and an ovarian tumor with melanoma in it, with adrenal metastases.

DR. RYDER: The presence of the lymphocytes was not overlooked. They were found in greatest numbers in the inflammatory tissue in the portal spaces, and we considered them part of the inflammatory process in the liver rather than an integral part of the tumor.

A REPLY TO DR. JOHANNES FIBIGER ON THE SUBJECT OF IRRITATION TUMORS

FRANCIS CARTER WOOD, M.D.

(From Columbia University, Institute of Cancer Research)

On December 8, 1920, at the request of Drs. Bullock and Curtis, I presented before this society a report of some experiments done in the Institute of Cancer Research on the artificial production of sarcoma of the liver in rats. That Dr. Fibiger received from the published account of these experiments the impression that Drs. Bullock and Curtis did not appreciate the importance of his work on *Spiroptera* cancer is evidenced by a letter received from him. Since he is displeased with their account it seems advisable to give to the society in his own words the corrections he thinks should be made in their statements:

DR. FRANCIS CARTER WOOD

Dear Sir: I have received the valuable paper of Bullock and Curtis: "The Experimental Production of Sarcoma of the Liver of Rats,"¹ and I beg you to accept my most hearty thanks for forwarding it to me.

I cannot, however, conceal that I have been highly surprised on seeing the incorrectness with which Bullock and Curtis have reported various particulars of some of my previous papers, and I shall therefore beg to address to you the following remarks, reserving, as a matter of course, my entering occasionally a public protest against the way of reporting used by Bullock and Curtis.

In the paper in question (p. 150) they write that "he (Fibiger) obtained 54 tumors (*Spiroptera carcinomata*) in the 134 animals which lived for 30 days or longer." In my paper: "Investigations on the *Spiroptera* Cancer III" (*Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser*, 1918), p. 17, I distinctly wrote that "out of the 134 rats which lived in the space of time concerned, 18 were subjected to no sufficient microscopical examination or to none at all." Thus, it was impossible to include these 18 rats in the table showing the frequency of the *Spiroptera* carcinoma (p. 18). The 54 tumors, then, were not found among 134 rats, as reported by B. and C., but among 116 rats, and it cannot be known whether or not carcinomata would have developed in the remaining 18 rats.

When the authors write further: "In 8 of the 84 cases he (Fibiger) observed lung metastases," this statement, too, is wrong. Pages 25-26 in

the paper quoted, the following passage will be found: "Altogether, in special examinations on metastasis formation, metastases have, thus, till now been found in 8 out of 33 rats, and in 2 of 3 white mice, mentioned above, in whose stomach *Spiroptera* cancer had developed." This permits of no misconception and it is beyond excuse when Bullock and Curtis are giving the number of the rats in which metastasizing carcinomata were found as being 8 out of 84, as my paper contains the statement: 8 out of 33, no special examination on metastasis formation having been performed in the remaining 51 cases.

But the errors of Bullock and Curtis still seem to culminate in the following passage (p. 152 of their paper). They write here: "Fibiger and Bang reported the development of 22 carcinomata and 2 carcinosarcomata in 26 (tar-painted) mice which lived six months or longer. Of these tumors, 6 metastasized in the axillary lymphnodes and 2 in the lungs, and 3 grew on transplantation. Thus so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable."

How the fact that malignant growths were produced in 24 out of 26 tar-painted mice can be characterized by Bullock and Curtis as a production of "a few tumors," must be completely inconceivable to any rational reader. But still worse is the next passage: "most of which are not transplantable." Page 23 of Fibiger's and Bang's paper quoted by the authors contains the following passage: "Attempts were made in 3 cases to transplant the developed carcinomata, but in 2 cases without success. In one case transplantation gave positive result." On pages 26-27 successful transplantation of a carcinosarcoma is reported, and on page 32, that transplantation experiment was effected with positive result in one case of tar carcinoma.

Transplantation experiments, thus, were made altogether in 5 cases, and in 3 of these with positive result, and it remains unknown whether or not the remaining 19 tumors (out of the 24) would have shown transplantability, transplantation experiment being not performed in these cases.

To any reader this will be quite clear. Bullock and Curtis, thus, impossibly can have any idea as to the frequency of transplantable tar growths, and their report concerning the transplantability of these tumors is perfectly wrong and misleading.

A correct description of the transplantation experiments made by Fibiger and Bang rightly ought to have run as follows: "Fibiger and Bang have made transplantation experiments only with 5 tumors, out of which no less than 3 were transplantable." That this number must be considered very great is an obvious fact, because transplantation of keratinizing tumors, as commonly known, will frequently meet with great difficulties (see Fibiger, *Investigations on the Spiroptera Cancer* VI, page 16, *Det. Kgl. Danske Videnskabernes Selskabs Biologiske Meddelelser*, 1919). Nevertheless, transplantation turned out successful with 2 out of 4 keratinizing transplanted tar carcinomata.

And Bullock and Curtis, no doubt, then would have omitted the point 8 of their summary, in which they speak of the "sharp" contrast of the transplantability of the cysticercus sarcomata with the "few" transplantable growths reported by other investigators.

I may add that the authors do not even mention the successful transplantation experiment made by Yamagiwa in a case of tar sarcoma of the breast of a rabbit, quoted in the paper of Fibiger and Bang. I beg you to be sure that these remarks are impelled not only by my personal wish to have a correct report of my investigations, but besides, by a regard for you yourself and for your Institute. Previously (in the *Journal of Cancer Research*) I have pointed out some incorrectness of Bullock and Rohdenburg's report of my former investigations, and I should now prefer to avoid a repeated criticism, which certainly would not increase the respect rightly due to Bullock and Curtis—in other respects—very valuable paper.

Seeing in the report of the discussion, held in the New York Pathological Society, the remarks of Dr. Rohdenburg on my slides (p. 173), "If you take some of his (Fibiger's) and put them beside ours without seeing the labels, I doubt whether you could tell which was which," I should be very grateful if you would kindly send me such slides, belonging to the experiments of Bullock and Rohdenburg, as are demonstrating the correctness of these words. Certainly, Dr. Rohdenburg has examined some microscopical preparations of mine, and I don't believe Dr. Rohdenburg should have made the mistake of saying or supposing that the changes found in my slides were all in every place meant to be carcinomatous. Several of these preparations only contain carcinomatous changes in a few distinct limited places of the slides. But according to the plates published in the *Journal of Cancer Research* changes of this kind have never been found in the experiments of Bullock and Rohdenburg.

Yours truly,
(signed) JOHANNES FIBIGER

Dr. Fibiger's erroneous impression is no doubt based somewhat upon a previous publication by Bullock and Rohdenburg,² which questioned, and quite justly, the proof of the malignancy of irritation hyperplasias when based on morphology alone. Since this paper was published, however, further experiments with *Spiroptera* and with tar have added convincing biological evidence that malignant tumors have been produced by these agents; yet despite this Murray and Woglom³ in a recent paper still repeat the caution that morphology is not a sure criterion of malignancy. Bullock and Curtis gave full credit to the several investigators who had produced malignant tumors by means of irritants, and it is to be regretted that there was any misunderstanding of their appreciation of the very great significance of these results.

The experimental production of cancer by irritants unquestionably opens a new field in cancer research, comparable to the

discovery of the transplantability of cancer, and it is unquestioned that Drs. Fibiger, Yamagiwa, and Ichikawa are the pioneers in the experimental production in animals of malignant irritation tumors.

But there are certain points raised in Dr. Fibiger's letter which are, in our opinion, the result of complete misunderstanding of the facts brought forward in our publication and require detailed discussion.

In reply to his criticism of Drs. Bullock and Curtis' treatment of his data dealing with the proportions of tumors and metastases, it should be explained that they treated his material exactly as they did their own. That is, the infested animals which survived to the cancer age were counted as negative unless there was known evidence that they were positive, even though they received only a macroscopic examination. In respect to their own data at least, it is certain that this is the fairer procedure. With the large amount of material handled in these experiments it would be humanly impossible to make a complete histological study of all the liver cysts in each animal autopsied. Therefore, reliance was placed chiefly on gross diagnosis confirmed in each case by microscopical examination. The parasite was removed from each cyst, and any cyst showing suspicious localized or diffuse thickening was preserved for microscopic study. A large proportion of the cysts which appeared negative macroscopically were discarded. A relatively small number, however, were retained and examined histologically in search of early sarcomatous changes. In this group a very few early sarcomata were found, but the proportion was small. Since malignant changes exist, before they can be recognized in the gross, as thickenings of the cyst wall, a few tumors were undoubtedly lost by discarding the animals in which no tumor or suspicious cyst could be recognized by the eye. However, since all the tumor-bearing animals and those with suspicious cysts were in the class examined, while the animals from which cysts were not examined appeared negative in the gross, it would be manifestly unfair to base the proportion of tumors only on the

former highly selected group. We naturally suppose that other investigators examine microscopically every suspicious lesion and discard only such animals as they believe to be negative.

Even the complete microscopic examination of every cyst from every animal autopsied would be an imperfect test of susceptibility, for in the observed cases the duration of the period of irritation associated with early sarcomatous transformation varied by seven months. The number of animals dead from other causes during this period, *i.e.*, from seven to fifteen months after infestation, which were negative at autopsy, but which would have developed tumors had they lived longer, is probably large in proportion to the number in which there was a malignant change in a cyst wall visible only under the microscope. That is, were it possible to make the complete microscopic examination of every cyst the error of counting certain susceptible animals as immune would be reduced but not eliminated. This type of error is inherent not only in all studies of susceptibility to irritation tumors but in nearly all studies of susceptibility to any particular disease. It is rarely possible to be positive that every negative individual is immune.

The culminating error by which Drs. Bullock and Curtis seem to have particularly offended Dr. Fibiger is the following statement: "Thus, so far a great amount of labor and a large number of animals have been required to produce a few tumors, most of which are not transplantable." This sentence, which is a separate paragraph, refers, as "any rational reader" will note, to all the investigations on irritation tumors cited and has no particular reference to Dr. Fibiger's experiments. At the time the statement was made we knew of only seven such tumors which showed growth on transplantation. This number includes the temporary growth obtained by Clunet,⁴ and also the "tar sarcoma" (myxofibrosarcoma mammae) of the rabbit produced by Professor Yamagiwa and his associates, to which latter tumor Dr. Fibiger refers in his letter. For the information regarding this transplantable tumor we were indebted to Fibiger and Bang⁵ (page 8) who must have obtained their information from a

letter to Dr. Fibiger from Professor Yamagiwa. There is no description of a myxofibrosarcoma mammæ in the paper⁶ referred to by Fibiger and Bang. This tumor no doubt is the one described by Yamagiwa, Suzuki, and Murayama,⁷ in a publication received since the paper of Drs. Bullock and Curtis went to press.

According to these authors the transplantation experiments resulted in a few small growths, none of them larger than a grain of rice, but some of these which were examined microscopically showed evidence of growth. Propagation beyond the first generation was apparently not undertaken.

We do not wish to overvalue the material developed by Drs. Bullock and Curtis in comparison with that employed by other investigators, but it should be stated that the liver sarcomata which arose in the walls of the *Cysticercus* cysts were not subject to the difficulties of transplantation which Fibiger admits in the transplantation of keratinizing tumors.

Of the 43 *Cysticercus* sarcomata tested by homoplastic transplantation, only 2 failed to grow progressively. Some of the grafts from 1 of these 2 tumors showed temporary growth, the largest reaching the size of a white bean. The rat bearing this primary tumor showed small metastatic nodules in the omentum. In the second case which failed to grow progressively on transplantation the tumor was infected and abscesses were formed at the sites of inoculation. That is, homoplastic transplantation of *Cysticercus* sarcoma is successful in a high percentage of cases.

A simple method of determining the malignancy of irritation tumors has been demonstrated by experiments described in a valuable paper recently published by Murray and Woglom.⁸ These authors relied chiefly on the progressive growth of autografts (artificial metastasis) as the criterion of malignancy. The vast majority of *Cysticercus* sarcomata perform their own autoplastic transplantation, as is evidenced by the very general occurrence of peritoneal metastases, and, hence, do not require homoplastic transplantation to establish their malignancy.

We have examined the microscopical preparations of *Spiroptera* cancer to which Dr. Fibiger refers in his letter. While in some areas these experimental tumors suggest a type of epithelioma which occurs in man, we would not feel justified in calling such lesions epithelioma merely because they show morphological resemblance to epidermoid cancers. They do not exhibit the unrestrained invasive growth that in itself is diagnostic of malignancy; rather, they are localized epithelial reactions which show in one or more small limited foci a suggestion of infiltrative growth associated often with some degeneration or keratinization of the epithelium. In our opinion at least, one of the lesions which Dr. Rohdenburg mentioned in the discussion referred to by Dr. Fibiger simulates epithelioma as closely as any of the nine preparations of Dr. Fibiger's which we have studied. This lesion was described and figured (Plate 14) in the paper by Drs. Bullock and Rohdenburg.² They believed that the morphological evidence obtained in their experiments and in the early experiments of Fibiger⁸ and of Yamagiwa and Ichikawa⁹ was insufficient for a diagnosis of malignancy when unsubstantiated by biological proof. As stated in the communication which Dr. Fibiger criticizes, and restated in the present paper, the malignant nature of some but not all the growths produced in response to irritation by *Spiroptera* and by tar has been demonstrated conclusively by metastasis formation and by transplantability. We agree with the statement of Murray and Woglom that "it would be hazardous and inadvisable to attempt to decide whether the new formations described by our predecessors are in every case rightly included in the malignant new growths or not. It is even probable that some of the tumors regarded as benign by them would, if tested by autoplasmic transplantation, have given evidence of progressive independent growth."

It is impossible to judge how important a rôle the interpretation of the lesions plays in the varying proportion of tar cancers reported by different investigators. In comparing their own results with Tsutsui's,¹⁰ Fibiger and Bang⁵ suggest that their relatively larger number of tar cancers may have been due to a dif-

ference in the tar used or to a difference in the susceptibility of the Danish and Japanese mice. Each of these factors may be partly responsible. Bloch and Dreifuss¹¹ have recently reported the isolation from coal tar of the agent effective in the production of tar cancer. It is possible that the proportion of this ingredient varies in coal tar from different sources. That there is in rats a difference in the susceptibility to *Cysticercus* sarcoma of strains and even of families within the same strain is already indicated by the experiments which Drs. Bullock and Curtis are carrying on, in which 440 of these tumors have so far been produced. A difference in susceptibility seems to be the most probable explanation of Schmitt-Jensen's¹² failure to produce *Cysticercus* sarcomata of the rat liver by experiments which in all essential particulars duplicated those of Bullock and Curtis.

In conclusion it seems to us that the several experimental methods of producing malignant tumors are supplementary and that coöperation between the investigators would prove advantageous in the solution of the problems which have already presented themselves in connection with these irritation tumors.

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ACTIVE IMMUNITY AGAINST EXPERIMENTAL
PNEUMOCOCCUS TYPE I PNEUMONIA IN
MONKEYS FOLLOWING INTRATRA-
CHEAL INJECTION OF VACCINE

RUSSELL L. CECIL, M.D., AND GUSTAV I. STEFFEN

In a recently published article, we have shown that three large doses of pneumococcus Type I vaccine injected subcutaneously at intervals of one week produce a complete immunity in monkeys against experimental pneumococcus Type I pneumonia. Furthermore, we showed that satisfactory immunity can be produced by several *small* doses of pneumococcus Type I vaccine if the injections were made intravenously.

We have recently studied the effect of pneumococcus Type I vaccine when injected directly into the trachea of monkeys. As in the previous experiments, three inoculations were made, separated from one another by intervals of one week. The skin over the neck of the monkeys was sterilized with tincture of iodine and the vaccine injected through the skin into the trachea by means of a hypodermic syringe. The doses used were 20, 40, and 60 billion, making a total of 120 billion of killed pneumococci. The volume of vaccine injected was, in every instance, one cubic centimeter. In these experiments, as in previous experiments with pneumococcus vaccine, the immunity of the monkeys was tested two or three weeks after the completion of vaccination. As in previous experiments, all monkeys were killed at the end of the period of observation, in order to determine the presence or absence of pneumonia.

The results of vaccination by the intratracheal route were entirely satisfactory. The three vaccinated monkeys remained perfectly well, while the control developed a mild but very definite pneumonia from which he recovered.

We are now attempting to vaccinate monkeys by spraying their throats with pneumococcus vaccine. This experiment however has not yet been completed.

The intratracheal administration of pneumococcus vaccine appears rational in view of the fact that pneumococcus infection usually takes place by this route. We have shown in previous articles that immunity against pneumococcus may exist in the lung when no protective substance can be demonstrated in the monkey's serum. In the experiments with intratracheal vaccine this same phenomenon was observed, namely—complete immunity against pneumococcus in the lung and the entire absence of protective substance in the serum of the vaccinated monkeys. The protection tests were carried out on mice in the usual way.

Discussion:

DR. HUNTOON: I think this work of Dr. Cecil's and Mr. Steffen's is an extremely important contribution, in that it points the way to the ultimate path of medicine, which will be to prevent instead of to cure. Many interesting points have arisen here, particularly the one as to whether this is the production of the so-called local immunity. Is it possible to produce a local immunity of some particular organ which is not enjoyed by the rest of the body? Bordet's work on dysentery brought up this old question again. In his work the mucous membrane of the gut produces an immunity against dysentery, but I remember that Dr. Zingher told us before this Society that he had failed to induce any such immunity. I shall be interested to see how the spraying experiments come out, because this would offer a method of easy application of vaccines, and it would avoid the use of the needle.

MR. STEFFEN: In the spraying experiment we are spraying the monkeys with an ordinary DeVilbiss spray, and we intend to continue the spraying about three weeks. This is a very easy method of vaccination, and it does not produce any reaction. The monkeys remain perfectly lively. Even when we injected twenty, forty and sixty billion killed pneumococci into the trachea they did not show any local or general reaction.

PRELIMINARY REPORT ON THE NATURE OF THE IMMUNIZING ANTIGEN OF PNEUMOCOCCUS. TYPE I

WILLIAM A. PERLZWEIG, PH.D.

The active immunity conferred upon white mice by the subcutaneous injection of heat-killed pneumococci (type I) and of various chemical fractions of the organism was studied. It was found that:

1. By using an initial small dose of vaccine followed by a larger dose a greater degree of immunity was produced in mice than by a single large dose or by repeated large doses of vaccine.

2. The nucleoprotein obtained from pneumococcus by treatment with anhydrous sodium sulfate (Rowland's method) or by alcohol precipitation from solutions of pneumococcus in bile salts carried the active antigenic fraction.

3. On autolyzing or digesting with proteolytic enzymes the entire organism or the protein fraction, the antigen was found in the digest unimpaired, being resistant to prolonged autolytic and tryptic action.

4. On the addition of the above digests to alcohol to make a concentration of seventy to eighty-five per cent. alcohol, the antigen was recovered in the alcoholic filtrate, but not in the precipitate. The antigen is not soluble in ninety-five to ninety-nine per cent. alcohol. The alcohol-soluble antigen is soluble in neutral, acid and alkaline aqueous solutions, but is not soluble in lipin solvents.

5. The antigen is not destroyed by boiling for five minutes if in neutral or slightly acid solution, but is impaired by boiling in alkaline solution.

6. The above methods of extraction of the antigen and the dependence of heat stability upon the reaction (hydrogen ion concentration) suggest the possibility of the antigen being closely related to the antineuritic vitamine, water-soluble B.

Further work on this subject is in progress.

Discussion:

DR. HUNTOON: This work of Dr. Perlzweig is revolutionary. I have known about it for some time because I have been doing somewhat similar experiments from a somewhat different angle. I can confirm a good many things that he has spoken of, and it has long been a belief of mine that we use too much antigen for the immunizing portion of the antigen is a very small part, and this can be proven mathematically. What he said about starting off with small doses is true. I have had a very wide experience with immunization of horses and I find that by giving a horse 0.1 c.c., which is a small dose in a 1,200-pound horse, then three days later 1 c.c., and then 5 c.c., you can get a horse up in three weeks as high as you can go. With

streptococci you can bring a horse up in ten days to that limit. If you start a horse with 5 c.c., you throw him out of condition, and get less antibody response. After you have once sensitized him you can go on. It seems to me that the aim of the bacteriologist who is interested in active immunity and protective inoculation should be to produce a non-toxic antigen which would give neither local nor general reaction, but which would give a rapid immunity. The difference in the rapidity of immunity produced by the injection of the whole organism and the injection of the extract is very considerable. In the one case it can be done in seven days. It is almost impossible to get a protection up to the same point by giving the doses of whole antigen extending over a period of three weeks. Why should the immunity in one case be much more rapid than in the other? You have taken the burden off the animal of disintegrating the antigen by putting it into a soluble solution so that it can be taken up by the cell that produces antibody. It is all a question of ferment action.

DR. PERLZWEIG: There are many intricate biological aspects of this problem that are quite difficult to solve, and which will require a good deal of time and labor. There is the question of the duration of the immunity after each of these antigens, which is a rather trying one. In some cases it seems to last quite well with the mice in question, and in some cases it does not last. Using a large number of animals, some succumb to a small dose of the infecting organism, while others, protected in the same way, withstand a very large dose of the infecting organism. I have had mice for two months after vaccination, some of which show a very good immunity at the end of that period, and others do not. There seem to be a great many factors to study that will require the exhaustive work of many men.

THE SKIN REACTION IN BRONCHIAL ASTHMA AND ALLIED CONDITIONS

NILS P. LARSEN, M.D., ROYCE PADDOCK, M.D., AND
HARRY L. ALEXANDER, M.D.

(From the Second Medical Division, Bellevue Hospital and Department of Medicine, Cornell University Medical College)

At the asthma clinic in the Out-Patient Department of Bellevue Hospital, observations were made on the "skin reaction" as a diagnostic aid in asthma and allied conditions. The mechanism of the reaction has not been established. That the skin reaction sometimes demonstrates the exciting cause of symptoms is a well-known fact. Since often no amount of questioning reveals the

cause and as the removal of it gives immediate relief, there is justification for continued study of the skin reaction as a diagnostic aid.

It is also well known that a certain proportion of individuals suffering with asthma or hay fever reacts by means of an urticarial wheal, when a small amount of the substance which can originate an attack is brought in contact with a scratch or injected into the skin. The wheal exhibits irregular edges, pseudopodia developing within twenty minutes, and is usually surrounded by an area of erythema, accompanied sometimes by swelling and other signs of inflammation. The site itches and occasionally remains red and swollen for several days. Regardless of method employed, a marked reaction in a definitely sensitive skin never is difficult to elicit.

Comparison of Cutaneous and Intracutaneous Methods.—More tests can be made with less trouble and time, at the same sitting with the cutaneous or scratch method. With dry preparations (used in the scratch method), however, there is no way in which to tell when they have lost their potency. With solutions (for intracutaneous injections), contaminations which destroy the potency can be readily seen. Also, when a precipitate forms in a solution, the potency may be decreasing. One such solution which had given very good reactions for several months developed a precipitate. Cultures proved it to be sterile. Upon testing, negative reactions were obtained in several skins which then reacted well to a fresh solution of the same protein.

Clinical results showed that the technical advantages of application in the scratch method were outweighed by the increased reliability of the intracutaneous method. To illustrate with a case: A. B. developed asthma only when in contact with horses. A horse could pass, or he could ride a horse for a few minutes without symptoms, but after close contact for four or five minutes, he invariably began to wheeze. On May 1, 1921, he was tested intracutaneously on the right forearm with a solution of horse dander prepared by Dr. Coca's method. Two inches away, on the same arm, a dry commercial preparation was applied by means of

a one-eighth-inch superficial scratch, upon which a drop of decinormal NaOH was applied, and then dry powder stirred into it. A control injection with horse serum was made. After twenty minutes, the intracutaneous reaction showed an irregular wheal 3 cm. by 2.5 cm., surrounded by erythema. The patient complained of itching at the site of injection. There was no reaction at the site of the scratch. The solution of horse dander, which gave this reaction, was controlled by injection into ten other asthma patients with negative results. The horse serum likewise gave no reaction. It was found that in fifteen similar instances, in thirty-one tests made, there was no definite response to the commercial preparation put on by the scratch method, although history of contact and intracutaneous methods were positive. The commercial dry preparations had been received within three months and then kept dry in the laboratory. The commercial pollen extracts gave a good reaction in most cases, whereas the dry products, especially the epidermal proteins, although effective in many instances, were so uncertain that they were unsatisfactory for routine use.

It is not possible to use the calibration devised by Walker in comparing these two methods. One can make no definite ruling as to the reading of reactions. The normal on an irritable skin cannot be compared with the normal on an unresponsive skin. It emphasizes the fact that the questionably positive reactions must be measured parallel with control injections on the same individual. These borderline reactions occur with the scratch as well as with the intracutaneous method. In such cases, an opinion can be arrived at only by repeated tests on different days, and with careful investigation of possible contact.

Comparison of the Two Methods with the Same Solutions.—To compare the scratch and the intracutaneous methods on the same individual with the same solutions, the following experiment was performed: Ten patients known to be sensitive to ragweed pollen were injected with three solutions of different strengths of this protein. These were freshly made solutions (Coca method)—Solution A, 1-100, Solution B, 1-1000, Solution C, 1-5000.

Weight of pollen in grams was the factor used in determining the strength of dilutions. The middle anterior one-third of the forearm was used, alternately placing the strongest solution superiorly and inferiorly on the different patients. Two inches away, and parallel with the injections, scratches were made about one-eighth of an inch long, and deep enough so that small red points were just visible. These scratches were kept covered with the various solutions for twenty minutes. The strongest solution was injected at the same time into two normal individuals, and had been used on many other patients routinely without reactions. Control solutions of other proteins had also been used on all these sensitive skins with negative results.

TABLE I

Comparison of Strengths of Reactions to Cutaneous and Intracutaneous Applications of Ragweed Solutions of Varying Pollen Content, in Ten Sensitive Individuals

| Solution | Positive | Doubtful | Negative |
|--|----------|----------|----------|
| <i>Solution A</i> | | | |
| Intracutaneous..... | 10 | 0 | 0 |
| Scratch..... | 4 | 0 | 6 |
| <i>Solution B</i> | | | |
| Intracutaneous..... | 6 | 2 | 2 |
| Scratch..... | 1 | 1 | 8 |
| <i>Solution C</i> | | | |
| Intracutaneous..... | 5 | 2 | 3 |
| Scratch..... | 1 | 0 | 9 |
| <i>Solution A</i> <i>Control patients</i> | | | |
| Intracutaneous..... | 0 | 0 | 20 + |
| Scratch..... | 0 | 0 | 20 + |

Solution A—Ragweed Pollen Solution 1-100
Solution B—Ragweed Pollen Solution 1-1000
Solution C—Ragweed Pollen Solution 1-5000

It is, therefore, evident that certain individuals, whose asthma or hay fever is brought on by specific proteins, may give a skin reaction to a solution of that protein when it is injected intracutaneously and show no reaction when the same solution is applied by means of a scratch.

Relation of the Size of Scratch to Size of Reaction.—To determine whether the size of the scratch influences the size of the reaction, the following experiment was performed: As in the above experiment, the middle anterior third of the forearm was used. Eleven patients whose skins were definitely sensitive to ragweed were chosen. Two or more scratches of lengths varying from 2 mm. to 11.5 mm., and just deep enough to draw blood, were made. The scratches were covered with decinormal NaOH and dry ragweed pollen mixed with the fluid. The reactions were read in twenty minutes. The size of reaction in breadth varies with the length of the cut, but not proportionately. For instance, a scratch 11.5 mm. reacted by a wheal 11 m. in diameter, whereas, in the same patient, a scratch 2.5 mm. long gave a wheal 7.5 m. in diameter; 1 : 1 vs. 1 : 3.

Schloss¹ believes that the size of reaction varies, depending upon the location on the arm. To test this statement, fourteen sensitive patients were given intracutaneous injections of ragweed pollen solution at the elbow fold anteriorly and a second injection of this solution, of like amount, was given 10 cm. below. The reactions were read in twenty minutes. The reaction at the elbow was never smaller, and was usually larger than the reaction at the region nearer the wrist. There was always more erythema at the elbow site.

Other Factors which Influence the Size of the Reaction.—The strength of the solution brought in contact with the cells is another factor which determines the size of the reaction. This is shown in Table I where the same amount of fluid was injected in each instance. This fact has been made use of to determine the initial dose of prophylactic injections. When different quantities of protein solutions of equal strength are employed, a similar relation is noted. Eight sensitive patients were injected on the right forearm with 0.01 c.c., and 0.04 c.c. of a ragweed solution containing 0.3 mg. of nitrogen per c.c. The reactions were measured at the end of twenty minutes. The size of the wheal was shown to increase with increase in the amount of protein solution injected, though not always in direct proportion to it.

The skin reactions were, therefore, found to be influenced by the following factors:

- (a) The preparation used.
- (b) The method of application.
- (c) The length of scratch made.
- (d) The site of injection.
- (e) The degree of cellular sensitivity.
- (f) The amount of protein in contact with the cells, and the amount of solution injected.

Local Skin Desensitization.—A point still in question is local skin desensitization. Mackenzie² showed that by repeated injections at the same site on the same day, he could cause a disappearance of the reaction. This was repeated on two cases, as follows: The first was a male nurse sensitive to timothy pollen. He was injected nine times in the same site with timothy solution, 0.6 mg. nitrogen per c.c. The first injection was given at 9:30 A.M.; the last at 6:30 P.M. The injections were approximately one hour apart. After no injection did the skin fail to respond with a new wheal. After the eighth injection, the patient had symptoms of hay fever; also, two hours after the ninth. The eighth and ninth reactions were the largest, giving wheals with irregular edges and pseudopodia. The next morning, the forearm was still red and swollen, and another injection at the same site was followed by a markedly positive reaction.

The second case was a ragweed-sensitive patient. Four injections were given during the course of an afternoon. After no injection did the cells fail to respond, and there was apparently no decrease in reaction.

To test out the effect of weekly injections at the same site, two patients were used. After several injections, there seemed to be a definite decrease in the reactive power of these cells. The wheal became smaller, the erythema less, and when seen on the succeeding day, the site of repeated injection was clear. The control injection at a new site showed a larger reaction. One patient was sensitive to both ragweed and timothy. Both decreased as stated

above, and when after three months the injections were reversed, the cells responded as at a new site. Injections were then discontinued for a period of three weeks. When the site was then reinoculated, it responded as a fresh site. On the following day, it was still red and swollen as badly as the control site. The effect of desensitization was apparently only temporary, and there was no permanent increase or decrease in the power of these cells to react.

References:

1. Schloss, O. M.: *Am. Jour. Dis. Child.*, 1921, xix, 433.
2. Mackenzie, G. M.: *Proc. Soc. Exper. Biol. and Med.*, 1921, xviii, 214.

Discussion:

DR. ZINGER: I am certain that we have all appreciated this interesting communication of Dr. Alexander. There are certain points that stand out in these intradermal tests in cases of hay fever and bronchial asthma that seem to me worth emphasizing. Anybody who has had the opportunity of seeing these tests carried out at the clinic conducted under the directions of Dr. Cooke and Dr. Coca at the New York Hospital will be impressed with certain facts.

The intradermal test seems to be highly specific. I recall just now an interesting instance of two children in one family, both of whom were suffering from asthma, and who applied for testing and treatment at different times at the clinic. In both children there was a marked reaction to an extract of rabbit's hair, and little or no reaction to the other tests. Inquiry showed that these children had slept on small pillows stuffed with rabbits' hair. Many cases of hay fever, also, give a strong reaction to a single pollen extract. This strong susceptibility is also evident in many asthmatics to individual epidermal extracts or cereal extracts.

Quite a number of these patients show a multiple sensitization to extracts from various groups; as for instance, the pollens, the epidermal extracts and the cereal groups. In some individuals one of these reactions seems to be most prominent, in others several reactions are equally prominent. I understand, however, that desensitization with an extract of the antigen that gives the most prominent reaction will also desensitize the patient against the other substances, to which he is sensitive.

The intradermal test seems highly sensitive. Many individuals give what are called negative reactions, although wheals varying in diameter from 0.5 to 0.75 cm. appear at the site of the test injections. Often it is difficult to decide whether the reaction is negative or moderately positive. Some individuals show equally prominent wheals at the site of all test injections. The diagnostic one when present appears distinctly enough as a very prominent wheal with peculiar pseudopodia prolongations. Owing to these doubtful reactions it seems quite important that fairly exact and equal amounts of the different test fluids should be injected.

DR. MACKENZIE: In the last few years there has been a great increase in the application of cutaneous reactions, and with the more widespread use, there has been a good deal of uncritical interpretation of the reaction. It is helpful and important to have such accurate observations as those which Dr. Alexander has reported to-night, and they are going to help clarify the problem. The procedure is simple, but the interpretation difficult. My experience with the cutaneous or scratch method and the intracutaneous method corroborates a good deal of what Dr. Alexander has said. There is no question about the greater delicacy of the intracutaneous test. Many patients will react to it, and not to the cutaneous test. I have in mind however, one experience which I think is worth remembering when doing reactions on patients who are highly sensitive. The patient was a sufferer from hay fever and bronchial asthma in the autumn. In doing a scratch test with a 1:100 dilution of ragweed there was only a questionable reaction. There was a little reddening, but not a definitely positive reaction. I then tried an intracutaneous test with a solution of ragweed containing 0.01 mg. of nitrogen per 100 c.c., made by extracting pure ragweed pollen with one one-hundredth normal sodium hydroxide. In a few minutes there was a large wheal four or five cm. in diameter. This went on for thirty minutes or so, and then began to subside. It was going down, and the patient had no further immediate symptoms. That night her arm swelled from the wrist to the shoulder; she had violent asthma, and broke out into urticaria over the entire body. She was confined to her bed for forty-eight hours.

As for the local exhaustion to which Dr. Alexander has referred, with Dr. Baldwin I have in press now a paper on that subject which reports observations made in the Presbyterian Hospital on a group of eight patients, repeating the test at the same site at short intervals. This was done by both intracutaneous and cutaneous methods. We found without exception that it is possible to exhaust the site locally, so that the reactivity is abolished. We found further that the exhaustion is much more rapidly effected with substances presumably more antigenic than ragweed extract. Horse serum and egg albumin have given the most striking exhaustion. However, even with our preparation of ragweed, which I presume is different from that used by Dr. Alexander, it has always been possible to exhaust the site locally, although it has taken a good many more applications than with such substances as horse serum or egg albumin. We have not tried the exhaustion method which Dr. Alexander reports, that is, repeating the tests at intervals of a week, but it is very interesting to know that at least a partial exhaustion may be accomplished in that way. I cannot feel that his failure to corroborate our observations on those two patients is of very great significance. The preparations are different, and it seems possible that exhaustion would have been accomplished if carried further. At any rate, our thirty-six consecutive attempts on eight hypersensitive patients exhausted the sites locally.

DR. THOMAS: Have you any theory to account for the variability in response to the tests for cutaneous sensitiveness, and have you noticed that patients during an attack of asthma are less sensitive to the proteins? Have

you any theory also to account for the fact that there is such a discrepancy in one patient's reaction to the same test from time to time?

DR. ALEXANDER: In regard to Dr. Mackenzie's remarks, we are apparently using ragweed solution made in a different way from his, so that may account for that discrepancy. I think he has more evidence than we have, as he has eight patients and we only have two.

As to the variability in these reactions, they are very delicate and variable in so far as constant results can be obtained. There are several different factors that influence the size of the reaction, as I pointed out, and after all when size crosses the threshold from a negative to a doubtful to a positive test one must be very careful in the interpretation of the results and comparisons can be made only by repeated drawings of the reactions. During an attack of asthma it is considered probable that these skin reactions do diminish. I confess it has been our experience that they are not completely wiped out, and an attack of asthma does not seriously affect the reaction. With the exhaustion from week to week we were able to reduce reactions very materially as compared to a control site on the same arm at the same time.

We also have had a few cases where the inflammation spread up the arm after intracutaneous tests. Walker describes similar experiences with the cutaneous method. In none of these has there been any permanent damage, although occasionally a temporary attack of hay fever and asthma has been induced.

TWO CASES OF HUMAN ACTINOMYCOSIS

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Actinomycosis in New York is not a common disease apparently, for there are records of only five clinical cases in Bellevue during the past fifteen years and among the last seven thousand autopsies in the Bellevue laboratories the two cases presented in this paper are the only ones on record. It is of course possible that one or two cases have not been diagnosed clinically but it is not at all probable that cases have been missed at the autopsy table, for sections from each case are studied microscopically.

The frequency of this disease in the United States may be judged from the fact that Erving¹ in 1902 was able to collect only one hundred cases, although the first case in this country had, according to Frazier,² been reported seventeen years previously, in 1885, by Murphy.

Actinomycosis is said to be more frequent in England and on the European continent. There were for example one hundred and thirty-five cases of actinomycosis in the London hospitals between the years 1902 and 1912.⁸

The first case to be presented is that of a male negro, aged forty-four, born and resident in the United States, a porter by occupation. He was admitted to a New York hospital September 2, 1920, complaining of pain in the right inguinal region of a week's duration. His family and past history were negative. Physical examination revealed some tenderness in the region of the pain and a marked psoas spasm on the right. The patient's temperature was 99° F. and the white blood cell count was 17,000 with 80 per cent. polynuclears. The condition was diagnosed as probably an appendiceal abscess that had ruptured retroceally. An operation the following day demonstrated a deep abscess in the right lower quadrant from which several ounces of pus were evacuated. The character of this fluid is not recorded. The surgeon found it "impossible to determine the source of the pus" but the process had extended dorsally to the posterior peritoneal lining and anteriorly to the face of the ilium. A smear of the pus showed short chains of streptococci. No growth resulted from an attempted culture.

After a convalescence not apparently unusual the patient was discharged, twenty-three days after admission. The wound had gradually closed and was not draining. The final diagnosis was, "Abscess of right inguinal region."

One month after his discharge the patient was readmitted, complaining of fever, saying that he was sick. Examination of the operation wound showed slight oozing of pus and there was again a marked psoas spasm. His temperature was 99° F. but rose that night to 101.6° F., returning to about 99° F. the next morning. At operation the day after readmission the granulating wound was curetted and a large cavity remained extending down to the brim of the true pelvis and up nearly to the attachment of the psoas. No cause was found for the failure to heal.

Blood chemistry was negative, the non-protein nitrogen being 32 mg. per 100 c.c., creatinine 1 mg. per 100 c.c., sugar 90 mg. per 100 c.c., and the blood Wassermann test was negative. The urine on readmission had been negative but a month afterwards it contained albumin in fair amounts. The patient was exposed to Roentgen and to sun rays. He was given massive doses of potassium iodide, but there was no improvement in his condition. For eight months he remained in this first hospital with continual drainage from the wound and a gradual failure of his general constitution. A diagnosis of tuberculosis was made, the focus being thought to be probably in the right kidney.

On June 22, 1921, the patient was discharged to Bellevue. This was ten months after his admission.

At Bellevue the man was seen to be markedly emaciated. He had a large granulating wound in the right lower quadrant with marked bulging. His lymph nodes were not palpable. The local condition was described as fol-

lows: "Large areas of protuberant granulations the size of one's hand. Tissue very soft and vascular and does not resemble chronic inflammatory tissue. It is not fibrous. It is possibly a new growth. There is much bleeding from the granulations."

A bacteriological report at this time was "prevailing organism a Gram negative, slender, non-motile, encapsulated bacillus growing readily in ordinary media but not characteristic of any known pathogenic organism."

Biopsy demonstrated "infected granulation tissue. There are some deep staining bodies suggesting actinomyces."

Repeated smears, however, did not reveal actinomyces.

A blood count showed white blood cells 7,000, red blood cells 1,600,000, hemoglobin 35 per cent. The urine contained albumin and pus.

Five weeks after admission to Bellevue the patient went into a delirious state and died. This was July 30, 1921, a year, lacking a month, following the onset of his symptoms.

The body was autopsied by Dr. Morton Ryder and myself and the following anatomical diagnosis was recorded:

Retroperitoneal actinomycosis invading the right ilium, the lumbar vertebræ (2, 3, 4, 5), the right kidney and the retroperitoneal lymph nodes. Localized pelvic peritonitis. Superficial ulceration of the bladder. Mural thrombosis of the inferior vena cava. Multiple infarcts of the lungs with gangrene. Renal calculus in left kidney. Hydronephrosis, bilateral. Hydro-ureter, bilateral.

"The external wound gapes widely and is filled with an exuberant growth of soft dirty brownish granulations flecked with brownish black spots. On opening the peritoneal cavity it is seen that the floor of the right iliac fossa bulges forward. The peritoneum covering it is thickened and gives a sense of fluctuation. The small intestine is moderately contracted and the coils of the ilium in the lesser pelvis are matted together by dense adhesions. An incision through the posterior peritoneum showed the fluctuant mass to consist of jelly-like yellowish material containing innumerable brownish granules the size of millet seeds. This extends inside the space of Retzius and posterior to the bladder beneath the peritoneum nearly to the midline. At this point the coils of the small intestine are matted together by dense adhesions. When they are separate an abscess cavity measuring about 5 x 5 x 1 cm., irregular in shape, is found containing greenish pus and completely walled off. The mass extends upward to the lower pole of the right kidney, which is normal in position. The tip of this pole is invaded by several nodules of soft yellowish tissue. The right sides of the second, third, fourth and fifth lumbar vertebræ are softened and black to a depth of a centimeter. The surface of the right iliac bone is bare in many places and is eroded, forming small pit-like depressions from one to several centimeters in diameter. The growth extends into Scarpa's triangle and the finger can be passed around the medial side of the femur below this.

"One or two lymph nodes in the right groin and one or two retroperitoneal nodes in front of the lumbar vertebræ are slightly enlarged, firm, and show yellowish tissue in the central portions.

"In the inferior vena cava is an adherent thrombus extending from just beyond the bifurcation upward four inches. This is about 5 mm. broad, 3 mm. thick, is yellowish and quite firm. It is smooth in some parts, granular in others and is firmly attached to the vessel wall.

"The mucosa of the bladder is diffusely reddened and over an area 2 cm. in diameter on the left side posteriorly it is roughened and black. At this site the matted coils of the intestine are adherent to the bladder.

"On section the lungs are pale red and are well aerated except in certain parts where the tissue is dark red, granular, and firm, and centrally is softened and brownish. These central areas have a foul odor and the degree of softening varies. The largest of these areas has a spongy necrotic center and the branch of the pulmonary artery leading to it is found to contain a firm yellowish thrombus lodged at the bifurcation with a prolongation running down into each branch. It is quite firmly lodged to the wall at the bifurcation.

"Microscopically the retroperitoneal tissue shows typical ray fungi in large numbers. They are immediately surrounded by polynuclear leucocytes and at a greater distance by vascular granulation tissue in which fibroblasts, plasma cells and lymphocytes are the predominating cells. A section of the lower pole of the right kidney shows typical ray fungi and in the wall of the inferior vena cava at the site of the thrombus there are typical ray fungi."

The second case is also that of a male negro. This man was twenty-five years old and had recently come from Panama. His occupation is not known. He was in coma when admitted to Bellevue and died a few hours later. The only history obtained was that he had recently come from Panama. Because his signs were obscure and his history unknown he became a case for the medical examiners of the city. A necropsy was performed by the Assistant Medical Examiner, Dr. Benjamin Schwartz, and I am indebted to him and to Chief Medical Examiner, Dr. Norris, for permission to present this case.

The necropsy demonstrated a bronchopneumonia and certain lesions in the liver, the ilium, the appendix and the colon as described below.

The liver was enlarged and was unusually adherent to the diaphragm. It was normal in color externally but the surface was bulging in one or two rounded areas. On section the parenchyma was found to be much reduced and there were present multiple abscesses varying in size from that of a pin head to one that was the size of an orange. These abscess cavities were lined by firm fibrous tissue. In some areas numerous smaller cavities had coalesced into one making the appearance that of a unique alveolar or honey-combed structure like "a sponge soaked in pus" to use Rolleston's description of a similar lesion. The lining tissue had a faintly yellowish tint. The pus from the abscesses was thick and viscid and yellowish-green in color. No granules were observed on casual examination. A methylene-blue stained smear revealed no typical picture although there were seen numerous homogeneous rounded bodies with suggestive feathery edges.

The wall of the colon was thickened and in places quite nodular. The mucosa presented numerous irregularly placed superficial round and oval ulcers not over 1 cm. in diameter. These apparently involved only the mucosa

and to a slight extent the submucosa. The edges were not raised or undermined and the ulcers were not typical of tuberculosis, typhoid fever or amœbic dysentery.

Externally the appendix, ilium and cecum were normal and their mucous surfaces showed nothing unusual.

Because a stained smear of the pus had been negative and because of the general characteristics of the lesions, together with the fact that the patient had recently come from Panama, a tentative diagnosis was made of amœbic abscesses and ulcers with actinomycosis to be ruled out microscopically.

Routine sections revealed typical ray fungi and no evidence of amœbic abscesses. The appendix was then sectioned serially and in the submucosa and muscularis was found an abscess extending longitudinally for a distance of about half the organ. No defect in the mucosa was demonstrated and the serosa was intact. The abscess appeared yellowish and granular with thin fibrous trabeculæ throughout. A similar abscess was discovered in the wall of the terminal ilium but gross serial sections of the colon did not reveal abscesses. Microscopical sections revealed typical ray fungi in the wall of the appendix and in the ilium. No ray fungi were found in sections of the wall of the colon. The possibility of the lesions in the colon being due to the actinomyces is greater because of the similarity between these lesions and those in a case described by Chiari^{2, 32} who says that primary actinomycosis of the intestinal tract manifests itself as a superficial invasion of the mucous membrane in the formation of whitish patches or in the more diffuse variety by the formation of nodules beneath the mucosa. These nodules undergo degeneration, ulcerate and rapidly extend. However since no ray fungi were demonstrated in the wall of the colon a diagnosis of actinomycosis of the colon can not be made.

Pus had been saved from this case and a more careful examination revealed characteristic granules. A majority of these were like sand grains in size and color. Some, however, were dark brown and some were sulphur yellow. All were soft. When some of this pus was shaken in a test tube of normal saline the grains were easily isolated from the viscid suspension and could be demonstrated clinging to the sides of the tube. Granules pressed between a cover slip and slide presented microscopically typical unstained mycelia. An anaerobic culture in dextrose agar had been made at the time of necropsy and a growth of *actinomyces bovis* was isolated.

In this case the primary lesion may very likely have been in the appendix if we accept the views of many observers. If so the fungi traveled via the blood stream to the liver.

The case illustrates the possibility of missing a correct diagnosis without particular care and special methods of examination. Pus in suspected cases should always be examined carefully for granules for it is very easy to fail to see them. The simplest method is to shake a small amount of the pus in a test tube of

water or normal saline. Having isolated a granule, it may be pressed between two glass surfaces and examined microscopically. Typical mycelia may readily be identified. Clubs will rarely be present in the human cases. A methylene-blue and a Gram stain will further aid in the diagnosis, but are confusing if applied to a smear of pus rather than to an individual granule that has been washed in saline. It should be remembered that the granules are by no means always the typical sulphur granules of the text-books. On investigation of the literature the following color designations were found applied to the granules: white,⁵ pearly white,¹ grayish white,⁷ yellowish white,¹ black,⁸ brownish black,⁷ brown,⁹ gray,¹⁰ pearly gray,¹ yellow gray,¹¹ cream colored,¹² red,¹³ yellow,¹⁴ sulphur yellow,¹⁵ lemon yellow,¹¹ whitish yellow,¹⁵ green.⁷

The granules have been described as granules, grains, specks,⁸ like sand,¹³ like minute pearls, like minute raspberries,⁹ like fish roe,¹⁴ like gun-powder,⁸ like rice particles,¹⁶ and they may be soft, firm or calcific.

The color of the pus has been described as white, cream, yellow, chocolate, and green.

Routine sections of tissue were stained with hematoxylin and eosin. Mr. Wm. Johnson, technician in the Bellevue laboratories, prepared other sections stained with carbol fuchsin, then decolorized and counterstained with picric acid. In these the ray fungus stands out as a red aster on a yellow background.

In none of the sections from the two cases presented were ray fungi seen with typical clubs. A typical actinomyces rosette is made up first of a central felt-like core of long, thin, branching filaments irregularly disposed but with a general radial arrangement and not decolorized in the Gram method of staining. Secondly, there may be at the periphery of the central core a crown of pear-shaped swellings of the terminal ends of the filaments. These are Gram-negative. Hiss and Zinsser⁴⁴ believe that they represent a form of degeneration and that they are the hyaline thickened sheaths of the threads. They are more frequently absent than present in the rosettes from man but are nearly always present in those from cattle. Thirdly, there have been described

coccus-like bodies that resemble spores and that led to the classification of the actinomyces as a spore-bearer. They are not spores, however, according to modern workers, but are either symbiotic cocci or else degeneration products.

Although the fungi in these cases did not show the clubs, they were typical in all other respects.

Conclusions:

In conclusion it may be noted that the chief problems in the study of actinomycosis are first as regards the method of infection and secondly as regards the method of treatment. Neither of these phases of the disease has been satisfactorily dealt with. Where the fungus is when not actively invading the tissues, how it gets into these tissues, whether it is a normal inhabitant of the various tracts of the body, whether it hides away in tonsils and dead teeth, all of these questions are as yet unanswered although there are many more or less attractive theories to explain them.

Finally, it should be emphasized that in every chronic suppurative lesion resembling tuberculosis, syphilis or a neoplasm, actinomycosis should if possible be carefully ruled out. This is especially true of atypical pulmonary disease where repeated sputum examinations should be made with a view to finding the ray fungus in the absence of the tubercle bacillus.

The diagnosis of actinomycosis is never established until typical ray fungi have been demonstrated. These may be found in tissue, in pus, in sputum, in urine, in feces, in spinal fluid, and most rarely in blood.

Discussion:

DR. HAAS: I happen to have at the present time a case of intestinal actinomycosis in a young man of twenty-one. He is dying now. The onset was almost identical to that of the case Dr. Russell described. He was first seen about two and a half years ago, when he gave a history of some abdominal distress during the previous week, and on the day of onset sharp pain in right iliac with nausea. When examined there was moderate shock, with a temperature of 100.5°. There was slight rigidity and tenderness of the right iliac region, and I decided it was probably appendicitis. Dr. Elsberg was called and that evening the boy was operated on. There was no inflammation of

the appendix, but the ilium near the appendix showed a perforating ulcer which was covered by omentum. There was some free sero-pus in the abdomen. At that time neither of us had any suspicion of what it was. Everything went along very well for a number of days, when after a rise of temperature a fecal fistula formed. This resisted all methods of treatment, and soon the subcutaneous tissue around the wound disappeared, and the skin with it, and there was an area about as big as the palm of the hand which was entirely exposed. At this time search was begun for the fungus, the differential diagnosis lying between syphilis, tuberculosis and actinomycosis. Nothing was found corroborative of any of these diagnoses. This condition continued for a long time, and it was then decided to remove the sinus. A second operation was performed and the sinus excised widely, and it seemed as though the result would be good. The wound healed very well, and just as the boy was to be discharged, the wound perforated, and the previous experience was repeated. As a matter of fact the fungus was not found until pus from a freshly perforating sinus was obtained. The boy now has five sinuses in his abdominal wall. It is only at the moment of perforation that one is able to find the fungus. Even after the character of the infection was known, examination of the pus failed to show the fungus again. The patient is now having very violent back-aches so that the vertebræ are perhaps becoming involved. So far as therapy is concerned, neosalvarsan, large doses of potassium iodide, methylene blue and emetine have been given, and as a last resort radium was tried, and that just about finished him. It was very interesting indeed to see how that treatment accelerated and intensified the progress of the disease. We have seen the same thing occur when the x-ray was used therapeutically in pulmonary carcinoma, the treatment producing intense toxemia and death within a short time.

DR. MOSCHCOWITZ: Actinomycosis is not as rare if you look for it. I have seen a considerable number of cases—a few of them in the lung, a very few in the abdomen, and a good many in the skin and bones. There is one point in connection with the diagnosis of actinomycosis which is emphasized by Dr. Libman, and that is that tenderness is a prominent symptom. We all know that the prognosis is bad. We hardly realize how bad it is. I have seen a number of patients in whom the lesion is apparently healed, and in whom months or years later either the wound breaks down, or a focus appears in another part of the body.

DR. RUSSELL: In regard to the frequency of actinomycosis observers differ. Dr. Moschcowitz, for example, states that he has seen a considerable number of cases and believes that the disease is not rare. On the other hand some observers have encountered it but rarely. Griffith⁴⁵ for example reports two cases as the only ones he has seen in fifteen years of active practice. He believes that the disease is rare and states that his colleagues have the same opinion.

In Bellevue as recorded above there have been only five cases in fifteen years. In the records of Roosevelt Hospital there is listed only one case. At New York Hospital there are only three cases in the records. At Bellevue

two cases have been autopsied in fifteen years; none have been autopsied at either Roosevelt or New York Hospital.

Undoubtedly cases are missed clinically but since all diseased tissues are sectioned at the post mortem table and a careful microscopical study made, it does not seem probable that many cases are missed that come to necropsy.

As to the frequency with which different parts of the body are involved there have been a number of reports. Ruhrah¹⁶ in his first report had collected 632 cases throughout the world and reported actinomycosis primary or maximum in

| | Per Cent. |
|-------------------------------|-----------|
| Head and Neck | 57 |
| Gastro-intestinal Tract | 21 |
| Thorax | 15 |
| Skin | 2 |
| Doubtful | 5 |

Later he¹⁶ had collected 1,094 cases with practically no change in the above percentages.

Taking the reports of six series of cases the following averages are obtained:

| | Per Cent. |
|---------------------|-----------|
| Face and Neck | 55 |
| Abdomen | 23 |
| Thorax | 17 |
| Skin | 5 |

In regard to the frequency with which the various organs are involved in the first place it may be noted that practically every organ in the body has been attacked by the ray fungus. But in abdominal cases the appendix and the cecum seem to be the site of election. Hinglais¹⁷ found the appendix involved in 60 per cent. of his cases. Kelley¹⁸ and Cope¹⁹ state that the appendix is the commonest site of infection, while Waring,²⁰ who reports seven cases, believes that the cecum is the commonest site.

Actinomycosis of the liver, according to Rolleston,⁴ is rare. He states that Auvray in 1903 could collect only thirty-one cases.

Secondary actinomycosis of the kidney has been repeatedly observed. Garceau²¹ for example reports 128 autopsies collected from various sources in which there was actinomycosis somewhere in the body and in eleven of these cases the kidney was involved. According to Ransohoff²² the only case of primary actinomycosis of the kidney was reported by Israel. In this case the organisms were identified in the urine and in pus from a lumbar fistula.

Robinson²³ in 1919 collected nineteen cases of actinomycosis of the female genitalia, reporting a case in which he found it in both ovaries in a patient fifteen years old.

Hodenpyle²⁴ collected thirty-four cases of pulmonary actinomycosis, and Hichens²⁵ gives a good account of this form of the disease.

The heart may be affected by metastases or by continuity.²⁶

Actinomycosis of the brain has been reported, but it is rare.²⁷

Cases have been reported involving the stomach,³⁴ gall bladder,³⁵ breast,³⁶ tongue,³⁷ larynx,³⁸ skin,^{16, 39} retina,⁴⁰ conjunctiva,⁴¹ salivary gland ⁴² and elsewhere.

As both Dr. Haas and Dr. Moschcowitz have observed, the course of actinomycosis is chronic. It is not infrequently recorded that after an apparently successful appendectomy, the patient, having been discharged as cured, will in the course of a few months to a year return with a draining wound or an abscess, and at this time a second operation and more careful examination will disclose the organism of actinomycosis in the pus.

The mortality is fearful. In Keen's surgery the mortality from all cases is given as 47 per cent. Frazier² says the mortality in cases of abdominal actinomycosis in the United States has been 71 per cent.

Jiron² gives the following mortality statistics:

| | Per Cent. |
|---------------------|-----------|
| Cerebral | 100 |
| Thoracic | 83 |
| Abdominal | 71 |
| Face and Neck | 11 |

So far no satisfactory treatment has been devised as the above mortality statistics demonstrate. Consequently every observer who has had two or more cases has experimented along lines of his own devising.

Potassium iodide is mentioned in all text-books but it has never been shown that there is the slightest scientific basis for the use of this drug which was introduced empirically by Thomassen²⁹ in 1885 for actinomycosis of the tongue in cattle and which was later proclaimed by Nocard¹² to be specific.

Harbitz and Gröndahl⁷ have demonstrated that the *actinomyces bovis* will grow luxuriantly on potassium iodide media in which the iodide is present in from 0.25 to 2 per cent. concentrations. Logically they doubt the value of this drug in the disease.

In fact potassium iodide may even be harmful. Jobling and Peterson³⁰ believe as a result of their experiments that the iodide neutralizes the action of the agents which prevent the solution and absorption of necrotic tissue and at the same time therefore lays bare to the action of the real germicidal agent the infecting organism that has been protected by the necrotic tissue. If this is true potassium iodide may accelerate this disease, for there is no known germicidal agent that can be administered to destroy the actinomyces in the tissues. Hence the organism may be speeded in its journey to other parts of the body.

Bevan⁴³ tried copper sulphate on the theory that it is effectual against vegetable parasites and he has had some success with it. Later he recommended using both potassium iodide and copper sulphate.

Many other drugs have been tried with occasional cures.

Autogenous and stock vaccines have been used.

X-ray and radium have been of some value apparently in a few cases. Heyerdahl³¹ reports six cases of cervico-facial actinomycosis cured by radium.

But in most of the series reported where various methods have been used the mortality has been in accordance with the average figures as given above, no matter what the treatment. For example Colebrook¹² advocates surgery plus vaccines. In his series, nine out of eleven cervico-facial cases were cured, all six of his thoracic cases died, and five out of the six abdominal cases died.

There is no doubt that effectual drainage should be established, but as to the medical and mechanical treatment beyond this there is confusion.

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ENDOCRINE GLAND STUDIES, INCLUDING GOITRE IN INDIA *

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I desire in the first place to thank you for the honor you have done me, and the Service to which I belong, in inviting me to speak to you this evening. I see in this audience so many whose researches have made their names familiar to students of endocrine disorder that it is with a certain diffidence I bring before you the results of my own investigations, carried out for the most part in the far distant Himalayas.

It is now some twenty years since Fate sent me to a part of the world where goitre was extremely common. I found myself, in 1902, posted as agency surgeon in hill stations situated in the Hindu-Khush region of Northern India, first in Chitral and later in Gilgit. The nearest railroad station is at Rawalpindi, some twenty days' journey by tonga, boat, horse and mule from Gilgit. One has, therefore, some excuse for speaking of one's work as having been done under isolated conditions. The facilities for intercourse with one's fellow-workers were, of course, very limited indeed; while access to medical literature was very restricted.

In Chitral and Gilgit goitre was so common that in some vil-

* Stenographer's report of a lantern slide demonstration given before the New York Pathological Society on November 9, 1921.

lages no one was free from it. In localities where its endemicity was high, men, women, and children alike suffered from it. In the village of Awi in Chitral, for instance, about sixty per cent. of the children were born with congenital goitre, while many were cretinous, and every man, woman and child was goitrous. The villagers used to say of this village that "even the trees had goitre"; there was some excuse for their thinking so, since many of the trees did have curious nodular growths on their barks. These excrescences arose, of course, from causes other than those which gave rise to goitre. The goitrous state of this village, which was not exceptional, gives an idea of the extent of the prevalence of the disease and of its congenital manifestations. But while it was so prevalent as this in one village, another situated, it might be, within pistol-shot of the first might have no goitre at all. This circumscribed distribution of endemic goitre has always been a very great puzzle.

When I first went to Chitral in 1902 most of the current views as to the causation of goitre centered around the water-supply; it was thought to be due to excess of lime or of magnesium in the water, or to be due to snow water. So knowing nothing, premising nothing, I began to occupy myself in the study of its etiology. The first observation of any importance which I made was as follows: There were on the Gilgit-Fan eight villages situated one above another on a single water supply. I made a survey of the endemicity of goitre in each of these villages. Every man, woman, and child was examined. It was found that in the first village there was eleven per cent. with goitre. The water was not confined to the banks of the stream, but was used to irrigate the cultivated land between the villages. The irrigation water joined the main stream at the second village, and in this village the percentage of goitre had risen to eighteen. The stream spread over the fields, irrigating them, and came to the third village where the incidence of goitre was twenty per cent. Below this point the main stream was joined by another of exceptional purity, and the fourth village showed a drop in the incidence of goitre to eighteen per cent. I need not continue with this de-

tailed description, but I will tell you that the incidence of goitre gradually increased until ultimately it reached forty-five per cent. in the eighth and lowest village on the common water-supply. This observation was made in 1906. Later Dr. David Marine, than whom there is no one who has contributed more to our knowledge of thyroid disease, made a similar observation with regard to artificially bred trout. He found that goitre gradually increased from above downwards in the tanks holding the trout, and that a diminution in the incidence of goitre occurred when the stream was joined by another water-supply. Since then I have pursued one line of investigation and Dr. Marine another, but to-day finds us in substantial agreement. I took the line that the increasing incidence of goitre in villages situated one above another on the same water-supply was associated with the increasing bacteriological impurity of the water. I thought that if this were the case, and if bacteria were concerned in the production of goitre, then the disease might be curable by intestinal antiseptics. Consequently, a man who had a well-marked goitre without adenomatous degeneration was given large doses of salol. After he had been taking salol for ten days or so and no appreciable improvement had been noted, I went on tour, leaving him still on salol. At the end of six weeks, I returned and found his goitre had disappeared. I then tried thymol in other cases, using the drug in large doses, and I got results with this drug which I will presently show you on the screen; they justified my assumption that bacteria in the digestive tract were concerned in the genesis of goitre.

Before I go on I wish to say a word or two about the goitres which one found in Chitral and Gilgit. In the first place, Graves' disease, or exophthalmic goitre, was practically unknown. I can count on the fingers of one hand the cases of Graves' disease which I saw among the indigenous inhabitants of Gilgit; and when one is dealing in thousands of cases of goitre that is a very striking thing. The cases of Graves' disease which I did see were definitely associated with fright or shock. Another point which I wish to make is this, that throughout India Graves' disease occurs

but rarely amongst the indigenous inhabitants. Some three or four years ago I sent a request to the great Presidency hospitals in India—at Calcutta, Bombay, and Madras—where the number of patients coming to the hospital in a year is very large, asking the superintendents to let me know the numbers of cases of Graves' disease admitted amongst various races of India during a period of ten years. They sent me figures which showed that it was very rarely found among the indigenous inhabitants, although it did occur amongst those who were strangers to the land—Europeans, Parsees—and was also comparatively common among Anglo-Indians. During the war, however, I came across a number of cases of Graves' disease among Indian troops who had been to Europe. It is a point of considerable interest that among men who had come from India, where Graves' disease is practically unknown, examples of this malady should have been encountered. It would seem that the conditions of service in Europe were such as to favor its development in Indians, who in their own country are rarely affected by it. I throw out the suggestion, therefore, that Graves' disease is a disease of civilization. Another point is this: almost all cases of goitre of long standing in Gilgit ultimately become adenomatous, and yet I never saw hyperthyroidism associated with thyroid adenoma. One reads a very great deal about "toxic adenoma." I have never seen it in the Himalayas.

With your permission I will now show you some slides. This one represents a goitrous patient who was the first man I ever treated with thymol. He looked after a herd of cattle and continued this occupation throughout the whole course of treatment. He came regularly to hospital for three and a half months. He had a goitre which caused the circumference of his neck to measure 42 cm. The next picture shows the same man after three and a half months' treatment by thymol, when his neck measured 36.5 cm. There is no doubt about the result. The man did his customary work; he was not a resident patient in the hospital, and to my knowledge he did not get any other treatment. I collected many more such cases. Messereli of Lusanne has pub-

lished many cases confirmatory of this action of intestinal antiseptics in recent cases of endemic goitre.

Now came the next step. I assumed, if I were dealing with intestinal organisms having to do with the causation of goitre, that I might get results by preparing vaccines from them, and treating recent goitres with such vaccines. Here is a picture of a man with goitre that had caused the circumference of his neck to measure 42 cm. before vaccine treatment was commenced. I gave him an autogenous *B. coli* vaccine in large doses once a week. Within a few weeks the goitre had disappeared. In those days my methods of standardizing vaccines were not so accurate as they would be to-day. I was probably giving this man much larger doses than I thought. He, as well as others similarly treated, had marked reactions after the injections. Here is another man who was treated by vaccines. This case is interesting, because the vaccine with which he was treated was made from a spore-bearing organism obtained from the fecal discharges of one of my polo ponies that had developed goitre. I injected it into this man in large doses. He was so greatly improved after several weeks' treatment as to show little trace of his goitre. These results were obtained with vaccines made from various intestinal bacteria. There was no specificity about their action.

I have shown you three or four of these cases, and I think you will have observed from the pictures that apart from the improvement in the goitre itself, the general appearance of the patients greatly improved. Any hypothyroidism which they may have had cleared up. The skin became much finer and softer, and the face thinner and less puffy looking,—a result noted also to follow cure by iodine, by thyroid extract, by soured milk, or by intestinal antiseptics. Precisely how large doses of vaccines may bring about this result, or what component of the bacteria is responsible for it, I do not know.

The next step in my work was to see whether I could induce goitre in man and animals. I have made a great number of attempts to do so. This picture shows the trachea with the attached

thyroids of a number of rats. The top row shows those of the control white rats. The second row shows the thyroids of wild rats from the locality in which the experiment was conducted. So you will see that the white rats did not have any goitre when the experiment was started. I got a large cage and divided it into three compartments of equal size; in each I put six white rats. In one compartment were the controls. In the second were rats which were fed on the residue left on the candle of a Berkefeld filter after filtration of a fecal emulsion from a goitrous person. In the third were rats which received the fecal filtrate. One hundred per cent. of the animals which received the fecal material developed goitre while the controls on the same food and in the same cage did not. The result of this experiment strengthened me in my assumption, which was becoming a belief, that goitre in Gilgit was intimately associated in its origin with bacterial organisms resident in the alimentary tract, and reaching the tract by way of water or contaminated food. At that time I only thought of such organisms as contributors of positive agents to the thyroid's harm. I could not think of them apart from the direct action of their toxins, so I believed for a time that goitre was caused by the direct action of microorganisms or of their toxins on the thyroid gland, and I continued my search for a specific bacterial excitant of the malady. I have altered that view to some extent; and have abandoned the view of a specific bacterial excitant, while still maintaining my position as to the important relation that exists between bacterial agents and the genesis of goitre and of thyroid disease in general.

Before starting these experimental investigations on a large scale, I had to establish a base line of normality for the thyroid gland of the animals (rats) with which I was working, because most animals kept in confinement showed some degree of thyroid change. What I did was to ask the plague medical officers to send me a large number of the rats which they caught in connection with anti-plague measures. They sent me some six hundred wild rats from various parts of India. I found some interesting things in connection with these rats. In those from the sea-coast

and from about the level of the sea-coast, the thyroid had in the majority of cases the appearance shown on the screen: the acini were well defined and distended with colloid, low cuboidal or flattened epithelium lined each acinus, and the organ was in its colloid or resting phase. On the other hand, a number of them were like this. The vesicles were smaller, the colloid was much thinner and less plentiful, the acinar cells were higher, and the gland was in a condition of physiologically active secretion. About twenty-five per cent. coming from the sea-level were of the latter type. When I examined the thyroids of rats from localities at a height of six thousand feet or more above sea-level, the greater proportion of them were found to be of the second type, that is to say, of a type which one associates with greater physiological activity. It seemed, indeed, that the farther from the sea-coast or the higher the altitude, the more physiologically active was the thyroid, an observation that may not be without significance in connection with the preference of goitre for mountain ranges.

The next specimen is a section of an experimentally produced goitre in a rat; you will see that there is evidence of marked hyperplasia; the amount of colloid is very small; the acinar cells are high; there is a tendency to acinar budding, and the thyroid is beginning to assume the histological characters which it is customary to connect with Graves' disease.

The next step in my inquiry was to see if I could produce cretinism and other congenital manifestations of thyroid defect; so I fed rats throughout pregnancy on fecal material or on bacterial cultures from the feces of goitrous persons. Here is a litter of three young rats aged twenty days. The mother of these animals was fed on milk and unleavened bread, and received the fecal filtrate from an emulsion of feces. The middle one is very much smaller than the rest. It has curvature of the spine and is but sparingly clothed with hair. After I had photographed this litter, the badly grown animal in the center was eaten by its parents. In order to avoid that risk in future I killed the young that were born to mothers fed on fecal material, four days after birth. This specimen shows a four-day-old litter, one of which is a cretin.

This is its thyroid and parathyroid glands. The gland was devoid of thyroid structure and was made up largely of connective tissue cells; the thyroid apparatus was congenitally atrophic and there was no evidence of vesicle formation nor of colloid. It was thus shown that there was something in the fecal material from goitrous persons which when administered throughout pregnancy to goitrous rats was capable of causing cretinism in the young.

The next specimen shows the effect of fecal anaerobes when fed to pregnant rats in causing hemorrhagic lesions on the parathyroid glands. I found such lesions as these in quite a high proportion of newborn rats whose mothers had received, throughout pregnancy, anaerobic cultures of fecal bacteria in glucose broth.

After dealing with rats I went on to larger animals. I procured from Delhi a number of female goats of the first year that had never had offspring. They were brought up to my laboratory, which was situated at a height of 6,900 feet above sea-level. Eight were kept as controls, and twelve were used for the actual experiment. Both controls and experimental animals received the same food; there was no difference in their intake of iodine. The only difference was that I muzzled a number of my controls so that they could not eat anything except what I gave them. I fed these goats for several months on cultures of fecal bacteria. On one day they received 10 c.c. of a 24-hour culture in 2 per cent. glucose broth, on the next a 48-hour culture, on the third a 72-hour culture, on the fourth a 24-hour culture, and so on. After several months the thyroids of most of them were palpable. They were then impregnated, and during pregnancy these cultures were continued. They gave birth to young that were all dead-born, hairless, and having enormous goitres. The controls on the other hand which received no cultures gave birth to kids that were fully developed and had excellent coats. Several among the control kids had small congenital goitres which disappeared shortly after birth and one was born dead but fully developed. The contrast was so great that it is impossible to escape the conclusion that the cultures referred to contained bacteria or their

products that greatly favored the development of congenital goitre and cretinism.

At one stage of the proceedings I took water from the last village on the Gilgit water-supply and passed it through the candle of a Berkefeld filter. Sixteen young men, including myself, drank, night and morning, under strictly controlled conditions, a cupful of the residue left on the candle of the filter. I had no medical colleague who could check my investigations, so I was forced to rely on a member of another profession—an engineer. I thought he would probably be capable of noticing any changes in the size of our necks. He measured my neck before the experiment commenced and after it was completed. At the end of the experiment he gave me a certificate which I came across among a lot of old records a short time ago. It said that I had a swelling on the right side of my neck, and a bridge of tissue across the windpipe that rose and fell on swallowing, and that neither of these were there two months before. So I think you can take it that I did have a goitre, as did also several of the others. The controls remained goitre-free.

Having thus produced goitre in man and in animals; having also produced the effects of thyroid deficiency in the offspring; and having cured goitre by intestinal antiseptics and by vaccines, the next step was to prevent it on a large scale. The opportunity presented itself when, in 1913, I was asked to report on a school just below Simla where goitre was extremely prevalent. This school is intended for the boys and girls of British soldiers who cannot be sent home to England for their education. They get an excellent education there, but unfortunately they suffered greatly from goitre. You will see from the chart which I now show you that among boys between five and ten years of age something like eight per cent. were goitrous. Among boys of sixteen and over, forty-three per cent. were goitrous. Among the girls the incidence of goitre was even more marked. In those between ten and fifteen years of age fifty-nine per cent. were goitrous, while sixty-four per cent. of the girls over sixteen were goitrous. This state of affairs was very serious, especially when

one knew, as I did then, that approximately five per cent. of all goitrous mothers give birth to cretinoid children. The boys and girls were in separate parts of the school; it was convenient to use the boys for the purpose which I had in view. I thought, after a study of the site and the water-supply, that the disease might be due to fecal pollution of the water; bacteriological examination every day over a long period showed it to be badly contaminated. Consequently I began to purify the water, using Nesfield's reagent which contains iodine. I used this reagent for about seventy-five days. After that I used chlorine. The water given to the boys was treated in this way. That given to the girls was not so treated. After six and a half months there was a drop from forty-three to twenty-four per cent. in the cases among boys, whereas among the girls, where the water was not treated in this way, there was a rise in the incidence of goitre. We reported on this observation, emphasized the beneficial effect of these reagents in the purification of the water as a means of preventing the disease, and recommended the continued use of chlorine as a purifying agent, or the introduction of another water-supply. It was ultimately decided to follow the latter suggestion. It may be that I laid too little stress on the specific effect of the iodine on the thyroid gland as an essential factor in reducing the incidence of goitre in this school. I have no doubt that a part of the good effect was due to the specific action of iodine, but equally no doubt that the removal of the bacterial impurity of the water was also concerned in bringing it about, for when a new water-supply was introduced the disease gradually disappeared. I have lately been officially informed that at the present time goitre is no longer prevalent in this school. The evidence that fecal pollution of the water had to do with the presence of goitre in this school is very strong. Dr. Marine's work, with which you are all familiar, shows the ease with which this very insidious disease can be eradicated by the prophylactic use of iodine. But this does not mean that the bacterial factor in its causation can be ignored, for it would seem that in the presence of certain bacteria in the alimentary tract more iodine is needed to

insure healthy thyroid action. The prophylactic use of iodine is a measure of the utmost importance. Anyone who has seen the moral and physical degeneration which can result from goitre must realize what a tremendously important thing it is that goitre should be prevented. We cannot as physicians emphasize too strongly the very great importance of preventing this disease in localities where prevention can be undertaken. It is a measure of the highest national importance in all countries where endemic goitre prevails.

We have then two important facts relative to the genesis of endemic goitre: first, that bacteria in the alimentary tract can be concerned in its genesis, and second, that small amounts of iodine will prevent it—extraordinarily small amounts. There must be some connection between these two facts. The ultimate cause of goitre is of course the undue stimulation of the thyroid gland consequent on the insufficient supply of iodine. I now think that this supply may be interfered with in a number of different ways: by insufficient intake of iodine, which is comparatively rare; by imperfect absorption of iodine; by insufficient assimilation of iodine; or by its imperfect utilization by the thyroid gland. It is within the orbit of these possibilities that we must seek for the true explanation of the influence of bacterial agents. It is to be remembered that goitre can and does arise in many cases where the provision of iodine is inadequate. Bacterial agents may act by preventing, in some way, the absorption, or by interfering with the assimilation of iodine, or by impairing the utilization of iodine by the thyroid gland.

The next part of my address will provide additional matter for consideration in this regard, and bring into prominence nutritional factors in thyroid disturbance. I wish now to show you some of my more recent work on the effects of faulty foods on the thyroid gland. This picture shows the normal thyroid gland of a monkey; contrast it with the next which shows the thyroid gland of another monkey that was fed for a considerable time on a diet of autoclaved rice and butter, that is to say, on a diet which is deficient in vitamins B and C, and disproportionately rich in

starch and in fat. The vesicles are small, the colloid is thin, and there is a great deal of congestion. The dark areas around the alveoli are distended blood spaces. That is an effect which I have noticed in a high proportion of animals fed in this particular way.

The next picture shows the normal parathyroid gland of a monkey. I wish you to contrast it with this which shows the intense congestion of this organ that is brought about as the result of a food deficient in vitamins and ill-balanced in other respects. You will remember that hemorrhagic lesions of the parathyroids can be produced in newborn rats by feeding their mothers during pregnancy on anaerobic cultures of fecal bacteria. Here is a similar result, but brought about by faulty food. It would seem almost as if the deficient food had enabled anaerobic microorganisms to exert their harmful effect on the parathyroid glands.

This chart indicates that the endocrine organs, with the exception of the adrenal glands and the pituitary body, undergo atrophy in consequence of a diet deficient in vitamins. The adrenal glands enlarge, and the enlargement occurs both in inanition and in that form of starvation which is known as avitaminosis. This dark column represents the average weight in milligrams of the adrenal glands per kilogram of body weight in control pigeons. This weight is approximately 93 mg. In pigeons that were fed on polished rice the weight of the adrenals reached as high as 160 mg.

The thyroid gland undergoes a considerable amount of atrophy in consequence of food deficiencies, so that their effect on one pair of organs—the thyroid and the adrenal—that are so intimately concerned with metabolic regulation, is to cause a diminution in the size of the former and an enlargement of the latter.

I will show another chart in order to emphasize a further point. This chart represents the effects on the thyroid and adrenal glands of pigeons of excessive feeding with mixed millet seeds, peas, and butter. In contrast to the effect of deficient feeding, the thyroid undergoes great enlargement, and the adrenals diminish in size. These organs are affected in a reverse order according as the food is deficient in certain essentials or excessively rich in other essentials. In the former case the adrenals enlarge and

the thyroids diminish in size; in the latter the thyroids enlarge and the adrenals diminish in size.

The next picture represents a section of the normal thyroid gland of a pigeon. It is one of the control pigeons referred to in the previous chart. Contrast it with this one which shows a section of the thyroid gland of a pigeon that was fed on a diet of mixed grains and butter. You will notice that the vesicles are almost filled with acinar buds, and that there is epithelial hypertrophy and scanty colloid. You will recall that this picture is one which is commonly recognized as characteristic of Graves' disease. Here is another one. You will notice here also that the acinar budding and epithelial hypertrophy are extreme and that colloid is scanty or absent.

Now we come to the effect of adding onions to this diet of mixed grain and butter. The effect of the onions is to reduce the incidence of the thyroid enlargement, the size of the actual goitre, and to alter, to a considerable extent, the histological picture from a hypertrophic to a more vesicular type. There is a considerable degree of congestion; the cells are not so high; acinar budding is much less pronounced, and there is rather more colloid in the vesicles. Here is another section which shows the same appearances. It would seem, therefore, that the histological character of the goitres produced in consequence of confinement, lack of exercise, contamination of the food and drink by fecal material, and over-eating of food excessively rich in fats, is capable of variation dependent upon the composition of the food eaten. This question of the effect of onions is a very interesting one, and very difficult to explain. It may be that their protective action against the hyperplasia induced by the excess of fats is due to the iodine-content of the onions. That I do not know, but I understand that a very small amount of iodine is present in onions, while some samples have none at all. On the other hand, it may have been due to their content of diffusible antiseptic. This antiseptic, as you know, has a wide repute in the treatment of purulent bronchitis. Onions are used by the native doctors of India in the treatment of cholera, and *succus alii* has a wide utility in

Western medical practice. It may be, therefore, that this anti-septic action came into play in the present instance. It is certain that the addition of onions to a dietary of mixed grains and butter would tend to alter the bacterial flora of the gastro-intestinal tract. Possibly their beneficial action may have been due to such an alteration; or it may be that all three of the possibilities I have mentioned were concerned in bringing about the beneficial result.

The more I work on the problem of the factors concerned in the production of goitre the less disposed am I to tie myself down to any single influence in its production. So far as simple goitre is concerned we must in the present state of knowledge take count both of nutritional and bacterial factors in its causation.

The next step in this study of the effects of fats on the thyroid was to ascertain what component of the butter gave rise to the thyroid enlargement. To that end I fed pigeons on a diet of mixed grains and oleic acid. The experiment was controlled by feeding at the same time other pigeons on mixed grains and butter, and others on mixed grains and cod-liver oil. This experiment was designed with the object of putting the animals under hygienic conditions favorable to the development of goitre. Two pigeons were confined in each cage, so that the amount of movement was very limited, and the fecal pollution of their food-supply was extreme. In this picture I show you the result of the experiment, which lasted 130 days. First of all you will notice the effect which non-hygienic conditions of life—lack of exercise, close confinement, contamination of food and water-supply by the animals' excreta—have in causing the enlargement of the thyroid gland. You will observe also that the addition of cod-liver oil to the food affords complete protection against these influences. Mellanby has noted the same effect of cod-liver oil in dogs. Next you will observe the effect of butter and of oleic acid in causing enormous goitres, especially in certain cases. In the case of butter the largest pair of thyroids weighed 950 mg., while the normal weight is approximately 25 mg. Both thyroids weighed rather less than one four-hundredth part of the total weight of the animal. This effect was produced by butter; it was also pro-

duced by oleic acid. The goitres produced by oleic acid are even larger. In one case the two thyroids weighed 1,050 mg., or considerably more than one four-hundredth part of the total body weight of the animal; so that I think one may reasonably say that whatever effect butter has in causing hyperplasia can also be produced, and with equal certainty, by the unsaturated fat-oleic acid. It would, therefore, seem that the injurious effect of the butter is due to its content of this acid.

Now we come to another matter. I desired to pursue the question of the relation of fats to thyroid hypertrophy somewhat further, and to examine it from the point of view of fat-excess and iodine intake. For this purpose I used tadpoles, since their sensitiveness to the influence of iodine might serve as an index of the harmful effect exerted by fat-excess on the thyroid gland. The first thing that I did was to find a food on which tadpoles would grow and flourish, and to which the fats to be tested could be added. A mixture consisting of caseinogen, 15 parts, white flour, 85 parts, and green pond weed, was found to serve these purposes. The flour-caseinogen mixture could readily be made up into pills, either with water or with the fats to be tested. These pills were dropped into the china vessels containing the tadpoles and were readily eaten by them. In the case of the cod-liver oil they ate greedily at first and but sparingly later in the experiment. The charts which I now show you represent the results of this experiment. The addition of cod-liver oil, butter, or oleic acid to the basal diet caused great retardation in the rate of the growth of tadpoles. The same effect was observed with lard, cocoanut oil, linseed oil, and arachis oil. This experiment lasted fifty-five days, and the actual weight of twenty tadpoles was plotted week by week. The next step was to ascertain what effect iodine would have when added to the diets that were excessively rich in fats. This chart represents the control experiment and shows the rate of growth of tadpoles receiving neither fats nor iodine, and of those receiving 0.5 and 1 mg. of iodine respectively per 3 gms. of food-mixture without fats. The next represents the rate of growth of tadpoles fed on a mixture containing oleic acid. This

dotted line represents the normal rate of growth in tadpoles receiving no oleic acid; the addition of 0.5 mg. of iodine almost completely compensated for the retardation of growth induced by the oleic acid, while 1 mg. of iodine did so completely. One mg. of iodine tended also to compensate for the retardation of growth induced by butter. In contradistinction to this compensatory action of iodine in the case of other fats, it will be noted that the addition of this amount of iodine did not compensate for the retardation of growth induced by cod-liver oil, but, indeed, further accentuated it. The more iodine one added to the cod-liver oil mixture the worse was the growth. I do not at the present moment wish to venture any explanation of these effects which, however, appear to be of much significance. It would almost seem that there is such a thing as a "fat-thyroid-iodine balance" and that a relative deficiency of iodine may be brought about in consequence of an excess of fat in the food and especially of the unsaturated oleic acid. If this be so it would provide an important example of a deficiency disease (goitre) due to want of one essential element of the food (iodine), resulting from excess of another essential food constituent (fat).

I have shown you the effects of deficient foods on the thyroids and adrenals of pigeons; it remains now to show the effects of deficient foods on animals more closely related to man. This chart shows the results of such foods as observed in monkeys. This column represents the normal weight of the adrenal glands in control monkeys; a diet which is deficient in all vitamins causes enlargement of the adrenal glands just as it does in pigeons. The thyroid atrophies, and there is a tendency to enlargement of the pituitary body, especially in males, just as there was in pigeons.

The next picture represents a cross-section of the adrenal gland of a healthy pigeon stained by osmic acid. It shows the normal proportion between the cortical and the medullary columns. The slide shows that in pigeons subjected to complete avitaminosis the cortical areas are greatly increased in consequence of the deficient food. There is at the same time a depletion of the cortical lipoids, as demonstrated by Cramer. I have shown that an in-

crease in the epinephrine content approximately proportionate to the increase in size of the glands occurs. This effect on the epinephrine content is seen in the blood pressure tracings from sheep. The next specimen is a section of a sympathetic ganglion attached to the suprarenal gland of birds. I show it to you in order to point out the degenerative changes that take place in the nerve cells of the ganglion in consequence of avitaminosis.

I find, gentlemen, that I have been talking for well over an hour, and that is quite long enough. I hope I have not kept you too long. It was by request that I inflicted the historical survey of my earlier work upon you, and as for my recent results I lay them before you so that you may for yourselves form your own opinion in regard to them. I have thought it best to present the facts as I observed them, and to refrain from attempting to interpret them, for, indeed, much work still remains to be done before their true significance can be appraised.

Discussion:

DR. MARINE: I really had not planned to say anything, but as Colonel McCarrison has been unkind enough to mention my name a number of times in connection with this work, I suppose I shall have to. It has been a great opportunity to hear a man talk who has really seen goiter. Most of us have never seen it. I have lived in the Lake basin about sixteen years, and I saw goiter there, but nothing remotely approaching what Colonel McCarrison has seen in the Himalayas. Truly that must be the most severe goiter district in the world.

I was interested in what Colonel McCarrison said about the morphology of the thyroid. Of course a great deal is written and heard about this, but I had hoped that medicine was over the stage of spending a great deal of time on the morphological variations in the thyroid. It is such a labile tissue that it may undergo morphological changes within twenty-four hours. It seems to me quite as labile as the blood tissue. To say that this change is typical of this disease, and that change of that disease I think is quite impossible, and I believe, although I have very few friends in that regard, that there are more people coming to that point of view.

Another thing which I did not know about before is that the incidence of endemic goiter in India bears no relation to the incidence of Graves' disease. In this country it does seem to bear a relation in a great many cases. Colonel McCarrison's explanation that Graves' disease is a disease of civilization is one that appeals to me. Both Graves' disease and simple goiter are increased in the Great Lakes district of our country. In the negro one rarely

sees exophthalmic goiter. I have seen several cases of it in mulattos. Colonel McCarrison's statement is interesting that Graves' disease is very rare in the natives in India, but may develop in those same natives when transported to the war zone.

The question of adenomas, the so-called toxic adenoma, is a very interesting subject. I have the feeling that the adenoma is of secondary etiological importance in the development of this peculiar syndrome or toxic picture. My experience has been somewhat similar to what Colonel McCarrison saw in India, that most endemic goiters eventually develop adenomas, and yet the incidence of toxic adenoma is exceedingly small. It seems to me that Graves' disease or toxic adenoma must be something more than the mere presence of an adenoma. That is the personal feeling I have.

Regarding the etiology of goiter, and with all due deference, I do not believe that water is the etiological factor. If water is related to goiter I believe it is due to the absence rather than the presence of something in it. On the other hand, the investigations which Colonel McCarrison has carried on with bacterial toxins seem significant to me, and there is no doubt there is some association when we remember that in infectious diseases the thyroid usually reacts. Why or how I cannot explain.

Another important point in the paper to-night is the observation that in inanition and in deficiency diseases in general the cortex of the suprarenal gland may undergo a most remarkable enlargement. That is a striking thing, but that is not all of it. The epinephrine content likewise is increased. I might digress just a moment to mention some recent work with the adrenal cortex. I have shown that if you cripple the adrenal cortex in a cat or a rabbit there is a remarkable increase in heat production which may last for months. That increase in heat production is associated with increased activity of the thyroid gland. If the thyroid gland is removed, and then the suprarenal cortex is crippled, you will not get increased heat production. There is some relation then between the suprarenal cortex and the thyroid gland which is a relatively new thing as compared with the older relation between the chromophil system and the thyroid gland. In other words, epinephrine will stimulate the thyroid gland. I think Dr. Goetsch will accept that. If we have shown anything it is that the suprarenal cortex also plays a rôle in thyroid activity.

The last point brought out was really quite new to me until recently, that is, the relation of fat feeding to the histological evidence of thyroid activity. Looking back over the work I have done in the last sixteen years it seems to me that I can see confirmation of Colonel McCarrison's results. In fish, for example, brook trout would get goiter when fed with pigs' liver. I have seen chicken farms that had to be abandoned because of goiter. I have seen several dairy herds in the Lake region where nearly all the calves were cretins with huge thyroid enlargements and these were fed with cotton-seed meal in large quantities. All these facts further indicate that there is something in the observation. How it operates is what I would like to ask Colonel McCarrison, but he has forestalled that question by saying that he has no idea.

Colonel McCarrison has stated that oleic acid is very potent in producing

thyroid hyperplasia, but that the administration of iodine with it markedly decreased this effect of oleic acid. I would like to ask one question. Have you worked with a series of fatty acids from the completely saturated fatty acids through oleic on to those very unsaturated fatty acids? I would like to know the effect of iodine in relation to the degrees of unsaturation. This is all a very interesting question, and we have no idea what it may be due to. It may have something to do with thyroid function and with alterations in suprarenal function, and after all we are trying to develop some of these interrelationships. Many people think it is very simple—that all you have to do is to put a few animals in a cage, use a little imagination, and a new relationship is established. I would like to put in a protest against what I am pleased to call "Endocrinology," because I do think it is criminal that a subject with such great possibilities should be exploited both commercially and scientifically.

DR. GOETSCH: I want to express my thanks to Colonel McCarrison and assure him of the great interest I had in listening to his presentation. I am not in a position to discuss his paper because my experiences are not as a rule with the simple goiters. These very rarely come to the surgeon, and my work is almost entirely with goiters producing hyperthyroidism. I was particularly interested in what Colonel McCarrison said about the occurrence of adenoma in India, and its percentage as compared with this very large number of simple goiters. I have always felt that the adenoma had no relationship to the same etiological factors on which simple goiter seems to depend, because of the fact that adenoma is a new growth. It is a benign growth. It is always encapsulated, and if it is not encapsulated, it is not an adenoma. Until we know what the cause of tumors is, we cannot say anything about the cause of adenoma. Then too the adenoma as far as I know has not been influenced greatly by any form of treatment with which I am familiar. The adenomas which I have seen are those which are causing hyperthyroidism. On a histological basis I think we have reason to say that the adenoma is responsible for hyperthyroidism of itself, because if you submit them to a very careful study for the presence of mitochondria, you will find that in every case of an adenoma associated with hyperthyroidism, the cells are rich in mitochondria. These mitochondria are excessively abundant, and if a section is taken from the thyroid gland just beyond the capsule of the adenoma, one finds that the thyroid gland itself has a colloid structure, in which one finds very few or no mitochondria at all. I have taken an adenoma from the side involved, and a wedge of tissue out of the opposite thyroid lobe in which one finds the same picture, and it seems to me that the cells of the adenoma, showing thus histological activity, are responsible for the hyperthyroidism present. I have tried to explain this colloid change in the gland outside of the adenoma on the same basis that Dr. Marine has caused the thyroid hyperplasia in his animals to revert to a simple colloid picture following the administration of iodine. I believe that the adenoma furnishes a toxic body which is closely related to thyrotoxin, and which is present in the body fluids in excessive amounts, and that the normal thyroid as a consequence reverts to a simple colloid picture very different from that seen in the ade-

noma. I have felt that if we were able to go back into these individuals after the excision of an adenoma we would probably find that this resting thyroid which before had a very simple inactive looking picture with the absence of mitochondria and the presence of fat would again take on an active appearance. In a simple colloid goiter the cells are filled with fat, and there is the absence of mitochondria. After the excision of the adenoma I believe this resting thyroid comes back to the normal picture again. I do not quite understand what Dr. Marine meant by saying that these simple colloid goiters might develop through all stages to the formation of adenoma and finally fetal adenoma. I do not know whether you meant the formation of these encapsulated tumors that have no relation to the thyroid as such, that can always be shelled out, or whether you meant those hyperplastic more or less circumscribed areas which one often sees.

DR. MARINE: I was speaking of all degrees of encapsulation.

DR. GOETSCH: These adenomas always have a definite capsular structure separating them from the normal thyroid, and one can see even microscopic adenomas, and from them trace their evolution up to those large ones with a capsule one centimeter thick. That is the adenoma I meet in my work. Of course those adenomas that do not produce symptoms of hyperthyroidism will not come to the surgeon for treatment, except when they produce symptoms of pressure.

COLONEL McCARRISON: Do you see a constant type?

DR. GOETSCH: We get every possible microscopic picture in adenoma, and I feel that being a tumor and arising from the fetal cells of the thyroid, it has the potentiality of developing into any histological type from the simple colloid to the higher degrees of hyperplasia resembling that seen in exophthalmic goiter. The fact that these fetal cells can reproduce any type of histological picture makes it very confusing and difficult to classify the adenomas. But when one applies the technique for the demonstration of mitochondria, then one finds that the simple adenoma without symptoms is relatively poor in mitochondria, and that the toxic adenoma, associated with definite symptoms of hyperthyroidism, is just as rich in these structures as exophthalmic goiter. If one applies the criterion of mitochondria one need not care whether the cells are tall or not, or whether there is much or little infolding. The presence or absence of mitochondria forms a better criterion of activity. In exophthalmic goiter the mitochondria are always present in large numbers. I have never had a case in which I have failed to find them. I have examined between three or four hundred. The adenomas are much more common of course.

DR. EWING: A countryman of Colonel McCarrison's said some time ago that medicine had passed beyond the descriptive stage, and was now engaged in quantitative measurements of the phenomena of disease. That may be true in certain very well known diseases, but we are still in the descriptive stage in thyroid diseases, and the observations which Colonel McCarrison has made illustrate the type of work by which successful research in this field may be conducted. I am greatly impressed by the ingenuity with which he carried on his work away out in northern India. It shows that when one

has the idea and the will the environment will lend itself. In regard to the practical aspects of this matter, I am extremely interested in the experiments with the thyroid and the adrenal, because they give one a new point of view from which to carry on work as a general pathologist. I have been looking at the adrenal for a good many years, without much intelligence, I must confess. We are getting information about the adrenal lately, and I find it possible to use a little more intelligence in the examination of this and the other endocrine glands at autopsy. I think in this way we are eventually going to get a basis on which to build up endocrinology and bring actual scientific facts to bear on many of these problems. I think the general pathologist has a function to perform here, so I want to thank Colonel McCarrison again and trust that his work will reach the fullest fruition.

DR. PAPPENHEIMER: It was not clear to me whether this hyperplasia of the adrenals is due to a specific deficiency of the accessory substances, or is merely an accompaniment of the wasting that one gets under those circumstances. Have you made any experiments in which the vitamine deficiencies were supplied, but in which the total food intake was insufficient? I should like to ask in this connection whether the cortical hyperplasia is due to a passive overloading of the cortex with lipoids mobilized during the process of acute inanition?

DR. OPPENHEIMER: I should like to ask what is the geology of that district in India, and just what is the history of the neighborhood.

COLONEL MCCARRISON: I do not propose to say much by way of reply except to answer the questions that have been put to me so far as I can.

As to the matter of the specific action of vitamins on the adrenal glands: An increase of the epinephrine content occurs in consequence of inanition. An increase of the epinephrine content occurs also in consequence of complete avitaminosis. No increase in epinephrine content appears to occur if vitamin A be supplied in the food. Associated with the hypertrophy of the cortex that results from avitaminosis, and coincident with the increased epinephrine content in the medulla, a depletion of the cortical lipoids occurs. Cramer has shown that the depletion of lipoids from the cortex is associated with the absence of vitamin A from the dietary. The absence of vitamin C produces some very curious effects. In guinea pigs fed on a scorbutic diet the adrenals are greatly enlarged; circumscribed areas of hemorrhage also occur in the cortex. I have never seen precisely this appearance in any other condition. The circumscribed areas of hemorrhage are distributed all around the adrenal cortex. The absence of vitamin A is associated with a great fall in the epinephrine content. The adrenal changes are among the earliest of the manifestations of vitamin C deficiency.

In regard to the question about the geology of the Gilgit district. I regret that I cannot rely on my memory at the moment for details regarding it. An account of its geology was kindly prepared for me by an eminent geologist who visited the district, and the matter is dealt with in my Milroy Lectures delivered before the College of Physicians of London in 1913. I would refer you, sir, to the original source for the answer to your question.

TUMORS (3) OF THE KIDNEY PELVIS AND OF THE URETER

P. W. ASCHNER, M.D.

We are all familiar with the ordinary papillary tumors of the bladder, and with the usual types of carcinoma of the bladder, but we are not so familiar with, and do not see so often, these types of tumors in the kidney pelvis and in the ureter proper. Within the last year we have had three such cases.

The first of these was a man of fifty with hematuria, who on cystoscopy showed a very small papilloma at the neck of the bladder, which was destroyed by fulguration. However his bleeding continued, and another cystoscopy showed blood coming down from the left kidney. Nephrectomy was contemplated, but the man had a cerebral accident just before operation, and died. At autopsy the specimen was removed. It was a large kidney, the upper half of the pelvis showing a diffuse papillary growth, not of great thickness, not invading the kidney parenchyma, nor the submucous tissues. On section it proved to be an apparently benign papillomatosis of the renal pelvis. The other kidney was found to be extremely small and insufficient in tissue, so that had the contemplated nephrectomy been done the patient would probably not have survived.

The second case was another of left-sided hematuria in a man of sixty-two whose kidney was explored, and at operation was found to be a small and apparently nephritic one. Decapsulation only was done. A year and a half later, owing to the recurrence of the hematuria, he was again cystoscoped, and sticking out of the mouth of the left ureter was a small papilloma. We concluded that this was an implantation growth, the primary one presumably being in the renal pelvis. The kidney and ureter were removed. The kidney contained in its pelvis a large tumor occupying the greater portion of the pelvis and its calices and invading the kidney parenchyma at the upper pole, with a number of small implantations along the course of the ureter. On microscopic section it proved to be a papillary carcinoma.

The third specimen is one from a man who had the typical history and signs of calculus disease of the right kidney. At operation a pyelotomy was done and the stones removed from the pelvis. At the site of the ureteropelvic junction a stricture was encountered. Because of the thickness of the tissue a small specimen was removed. We were much surprised to find that this was a squamous-celled carcinoma, primary in the ureter. The kidney and ureter were removed at a secondary operation immediately after the diagnosis was made. In addition to the ureter lesion, he had a very interesting condition. It was leukoplakia of the pelvis, chiefly in the lower of the two pelves which the kidney presented. The man has been well since except

that he has the leukoplakia in the bladder. The association of leukoplakia with cancer is well known in the tongue and the bladder, and I have looked through the literature and found no case of leukoplakia associated with carcinoma in the ureter. I am not convinced that it is on a leukoplakic basis *per se*. The ureter itself does not show a leukoplakic condition, and it is conceivable that he had a stricture at this point in his ureter, and that some of the leukoplakic material passed from the pelvis of the kidney, became caught at this point, and developed into a carcinoma.

I present these as three rather interesting unusual kidney tumors. It is interesting that fragments of the pelvic tumors are apt to break off and implant themselves in the ureter or the bladder. Such a growth in the bladder misleads one into believing that the bladder tumor is the cause of the hematuria. The case of squamous-celled carcinoma of the ureter is exceedingly rare. I have found only three in the literature, and of all primary tumors of the ureter, there are only about fifty on record.

Discussion:

DR. MACNEAL: I think it is a very interesting suggestion, made apparently without reservation, that secondary tumors arise in the ureter and in the bladder by implantation after transportation through the urine itself of particles of primary tumor from the pelvis of the kidney. The proof that implantation takes place in such a manner is rather difficult to furnish. I am not sure that it is generally accepted that this does occur. One has to think of other possibilities; there may have been perhaps a simultaneous development of tumors of the same type in various portions of the urinary tract. Also, one should perhaps think that the tumor may have metastasized through the lymph stream rather than through the lumen of the ureter itself. It is difficult to decide between these possibilities. The question of the implantation of tumors, especially the implantation of malignant tumors, or their metastasis by other routes than through the blood or lymph stream or by immediate contiguity, is unsettled in pathology.

Recently we have seen a case in which papilloma of the pelvis of one kidney was present, and this was removed. Some months later the patient returned and had a papilloma removed from the rectum. There was a difference of opinion between the surgeons in this case as to whether the papilloma of the rectum might not be regarded as in some way derived from the papilloma in the kidney pelvis. The histology of the second specimen was that of the usual papilloma which occurs in the rectum, and it did not resemble that in the kidney pelvis.

The tendencies which exist in epithelial surfaces to develop papillary tumors have to be recognized as a tendency which may be common to a considerable surface of the epithelium, and the question as to whether the second

tumor is an implantation of the first is a question about which we should keep an open mind in the present state of our knowledge.

DR. ASCHNER: The points made are very pertinent. We have a certain amount of clinical as well as pathological evidence that papillomata, particularly in the genito-urinary tract and probably in other parts of the body, can arise by implantation not through the lymphatics and blood stream. To my mind it is inconceivable that a papillary tumor at the neck of the bladder can come from the pelvis of the kidney by the lymphatics, because the lymphatic stream is in the other direction. I doubt if it would arise through the blood stream, because these tumors are very superficial things. It is not a malignant tumor in the sense of spreading by metastasis, but it can spread by implantation. In papillomatosis of the bladder that is true. You may observe a papilloma in the bladder near the ureter orifice and some time later see another at the fundus of the bladder. That is called a "kissing" lesion, for when the bladder is empty the fundus meets the trigone. The same thing is seen in tuberculosis of the bladder. We know that a bladder papilloma may be operated on, and all the tumors apparently removed; if the greatest precaution is not taken the patient may develop a growth in the suprapubic wound and along the course of the incision made in the bladder at the time of operation. That is one of the reasons why we cauterize the line of incision after the operation. I think these facts offer considerable evidence to show that papillary tumors of this type can implant themselves.

ANEURYSM OF THE HEPATIC ARTERY

WILLIAM FRIEDMAN, M.D.

(From the Pathological Laboratory of Mount Sinai Hospital, New York City)

The patient, 57 years old, born in Russia, house-wife, was admitted to Mount Sinai Hospital on the service of Dr. A. V. Moschcowitz on July 16, 1921, with the following history:

Seven years ago she was operated upon for gall-stones at the Beth Israel Hospital. A cholecystectomy was done and the patient had an uneventful recovery. Six years ago she had an attack of severe colicky pain in the epigastrium radiating into the back and accompanied by vomiting which lasted for several days. During the week previous to her admission she had again suffered severe colicky pain in the epigastrium which radiated to the back. She had several such attacks during the week. Most of the attacks were accompanied by vomiting. Twenty-four hours before admission the patient noticed that she had become jaundiced. The only other important symptom in the history was nocturia for six weeks previous to admission.

The physical examination revealed an obese middle-aged woman, intensely icteric and acutely ill. There was marked tenderness and rigidity

over the entire right side of the abdomen, especially in the right upper quadrant, but no rebound tenderness. The liver was palpable 4 cm. below the costal margin on the right side. The edge was sharp, the surface smooth. There was a moderate leucocytosis and secondary anemia. The stool contained blood, but no bile. Blood Wassermann was negative. The blood chemistry showed urea nitrogen 56, incoagulable nitrogen 109. Her temperature varied between 99 and 100, and the pulse between 96 and 100. Respirations were 24.

Two days after admission the patient passed a large stool consisting entirely of old fluid and clotted blood. Her condition became worse and operation was decided upon. The operation was performed by Dr. Aschner. The omentum and transverse colon were found densely adherent to the abdominal wall and under surface of the liver. The intestines were plum colored. The common bile duct was found markedly dilated and when aspirated yielded a small amount of blood. Upon opening it several large blood clots were found. The right hepatic duct was probed and found free. The left hepatic duct when probed yielded profuse bleeding. Some obstruction was met in probing the common duct toward the papilla. A duodenotomy showed the papilla to be normal and a probe could be freely passed into the common duct. The surface of the liver showed no irregularities. A tentative diagnosis of carcinoma of the left hepatic duct was made. The patient died several hours after the operation.

Autopsy revealed a most intensely icteric middle-aged woman. The heart showed some irregular atherosclerotic thickening of the mitral cusps. There was also marked atherosclerosis of the aorta. The peritoneal cavity contained no free fluid. The liver weighed 1,830 gm. The gallbladder was missing, having been removed at a previous operation. On probing the right and left hepatic ducts a large amount of clotted and fluid blood exuded. Just posterior to the right hepatic duct was found a spherical aneurysm about 0.75 cm. in diameter. The aneurysmal sac was filled with an organizing thrombus which protruded through a defect in the right hepatic duct. The common and hepatic ducts and their smaller radicals were distended with blood throughout the entire liver. The intestines contained a great deal of old blood. Microscopically the hepatic artery and all its branches showed marked atherosclerotic changes. There was found a generalized atherosclerosis throughout all the medium-sized systemic arteries which were examined.

Up to June, 1921, there were fifty-four cases of hepatic artery aneurysm reported. The disease is more common in males. Grunert believes 75 per cent. followed acute infections. Roland is of the opinion that as high as 20 per cent. are due to syphilis. Among other etiological factors are gallstones, and trauma at operation. There are two varieties: extra-hepatic and intra-hepatic, the former being more common. It occurs most often in the main branch of the hepatic artery. They may be multiple.

Hoeglar believes that 50 per cent. of the aneurysms are mycotic in origin. Usually the vessels in the liver show thickening of the intima and media. Ledieu reported one case in which there was healing of the aneurysm. Death is usually due to rupture of the aneurysm into the peritoneal cavity, the biliary passages, the stomach or the duodenum. The pressure of the aneurysm on the biliary ducts is supposed to be the cause of jaundice.

In view of the history of this case, of an operation for gallstones seven years previously which was followed a year later by a severe attack of abdominal pain similar to the one which initiated the patient's final illness, the possibility must be considered that the aneurysm was due to weakening of the vessel wall as a result of trauma or of infection at the time of the operation. In view of the extensive general atherosclerosis throughout the body, in which the hepatic artery had proportionately shared, a weakening of the wall as a result of this process must also be considered. Investigation has revealed that there was no unusual trauma or infection at the time of operation and it would, therefore, seem that the aneurysm of the hepatic artery was due to an atherosclerotic change within the artery with subsequent rupture of this aneurysm into the right hepatic duct and death due to hemorrhage.

Discussion:

DR. G. A. FRIEDMAN: I was very much interested in the case of Dr. W. Friedman and in his excellent presentation of it. I would like to mention that about nine years ago I had a case in which I made a tentative diagnosis of aneurysm of the hepatic artery. A report of the case with operative findings was published at the time. I shall refer to the history later. The patient was operated upon by Dr. Arpad Gerster, April 9, 1912. These were the findings at the operation: "As soon as the margin of the lesser omentum was exposed, the artery became visible as a pulsating cylindrical body, having the diameter of a large goosequill. It formed a loop with its convexity downward. Its proximal continuation could be distinctly followed by palpation of the celiac axis, this forming a large loop with its convexity pointing upward, so that the whole vessel, as far as visible and palpable, represented a large Roman 'S,' its entire estimated length being six inches. A marked whirl could be felt on the gentlest contact with the vessel. The gallbladder was normal, moderately distended with bile, easily expressed into the common duct. The common duct was not distended and contained no stones, no palpable tumor, no cicatricial ulcer, absence of stone in the gallbladder.

"All the exposed structures, especially the duodenum, showed marked cyanosis, charged to the bad anesthesia. The margin of the liver was markedly rounded and thickened, free from cicatrices. The stomach was much dilated by gases which were withdrawn with a tube. The index finger could be easily invaginated into the pylorus." The division of the aorta into the iliacs, instead of corresponding to the fourth corresponded to the second lumbar vertebra. The calibre of the aorta and iliacs and the coronaries of the stomach was normal. "Diagnosis—Dilation and elongation of the hepatic artery. No aneurysm." I quoted in my paper Kaufmann, who says: "Dilation of an artery, also called arteriectasia, may be diffuse or circumscribed. Some authors call only the latter aneurysm, but this is in an error: there are transitions between the two forms."

Dr. Gerster himself called my attention several months later to an article which appeared in a journal, edited by Professor Garé, in which my case was quoted as follows:

"In a woman of about thirty-five years old, who gave a history of excessive use of alcohol, the following symptoms were noted: severe paroxysmal pain in the right hypochondrium which became more intense in prone position, visible pulsation over the region of the liver, a subjective sensation of throbbing in this area. Lower border of liver was palpable. Diseases like gallstones, duodenal ulcer, tumor, visceral arteriosclerosis, cirrhosis of the liver, aneurysm of the aorta were ruled out. A diagnosis of aneurysm of the hepatic artery was made and the diagnosis was confirmed through exploratory laparotomy."

Three years later Professor Alb. Narath of Heidelberg, in discussing in his paper the necessity of ligating the hepatic artery in aneurysm, refers to my case as follows: "What happened in Friedman's case should never occur again. One should not satisfy himself with an exploratory incision in this condition, simply leaving the patient to his fate." I believe therefore that my case was an aneurysm of the hepatic artery. What became of my patient I do not know. I saw her seven months after her operation: her complaints and the clinical picture remained practically the same as before the incision.

In concluding I would like to say a few words in regard to Dr. W. Friedman's paper. It is possible that his patient had already her aneurysm at the time when she was operated upon at The Beth Israel Hospital for gallstones, because in the literature cases are recorded in which gallstones and aneurysm of the hepatic artery were found simultaneously. That the latter condition has a chronic course, over a period of years, is known to anyone who has looked up the literature of the subject.

DR. ROSENTHAL: Were the other vessels in the case of Dr. William Friedman investigated in reference to periarteritis nodosa?

DR. WILLIAM FRIEDMAN: The vessels were investigated with that in view. Teacher and Jack about a year ago published a case of hepatic artery aneurysm and reported a lesion which looked very similar to the lesion found in periarteritis nodosa. In this case we found no such lesion.

CALCIFICATION OF THE PERICARDIUM

A. WINKELSTEIN, M.D.

(From the Pathological Laboratory, Mount Sinai Hospital, New York City)

The specimen is the heart and the pericardial sac from a male patient 39 years old who was admitted to Mount Sinai Hospital in June, 1921. Ten years before, following an attack of rheumatic pain in the left arm, he was admitted to the Presbyterian Hospital with cardiac symptoms—chiefly dyspnea, palpitation, and edema of the lower extremities. He recovered in eight weeks and remained without symptoms until three years later, when he had a similar attack lasting five weeks. Following this he was well until two months before admission to Mount Sinai Hospital. His complaints then were dyspnea, cough, anorexia, weakness, epigastric pain, and edema of the lower extremities. The physical examination pointed to a cardiac decompensation due to aortic stenosis and mitral stenosis with insufficiency. Furthermore, on account of a continuous fever, irregular chills, and the occurrence of numerous white-centered petechiæ in both conjunctivæ and in the skin generally, an active subacute bacterial endocarditis was suspected. Four blood cultures, however, were negative. A broncho-pneumonia was also present. Three weeks later he went into a stupor and died. Briefly then, this case was one of cardiac insufficiency probably due to rheumatic valvular defects and possibly complicated by an active subacute bacterial endocarditis.

The post-mortem findings were very interesting. There was broncho-pneumonia, old right pleural adhesions, and an enlarged, granular liver, showing microscopically perilobular cirrhosis, and chronic passive congestion of the spleen, kidneys, and intestines. The coronary arteries and aorta were negative. The pericardium was universally adherent to the surrounding structures.

The heart with the pericardium weighs 1,100 gm. and appears like a huge *cor bovinum*. The visceral and parietal layers of the pericardium are universally adherent and thickened. In the region of the atrio-ventricular grooves the thickening amounts to several centimeters. Here it is densely infiltrated with lime so that a bony hard ring almost completely encircles the heart. This calcification extends for a distance of a few centimeters down on both ventricles and up on both auricles. On cracking open this ring small cavities are found in some places which are filled with cheesy, caseous material or thick pus. Both auricles are tremendously thickened and dilated. There is a moderate hypertrophy and dilatation of the right ventricle and a huge hypertrophy and dilatation of the left ventricle, the myocardium here measuring 3.5 cm. in thickness. There is a moderate stenosis of the tricuspid valve due to thickening and fusion of the cusps and a very marked mitral stenosis, the aperture of the valve admitting only the tip of one finger. The bases of the mitral valve cusps are infiltrated with lime. On the auricular aspect of the mitral valve, there are two irregular fissures covered with blood

platelet thrombus (the probable source of the petechiæ). The aortic cusps are so thickened, fused, and infiltrated with lime, as to form a moderate degree of stenosis as well as insufficiency. The myocardium is normal in color and presents grayish streaking.

The radiograph of the excised heart and pericardium reveals the calcification so exquisitely as to give one a false impression of overlying ribs.

Microscopically the pericardium shows a thick layer of scar tissue in some places and marked deposition of lime in others. Also within the calcified areas, scattered here and there, small areas of bone formation are found. There are also large areas of purulent infiltration which have a tendency to invade the myocardium. No tubercles are seen. The heart muscle is markedly hypertrophied and there is a moderate amount of perivascular and interstitial fibrosis. Bacteriologically, smears, cultures, guinea pig inoculation from the pus and tissue stains for the usual bacteria and for tubercle bacilli all proved negative.

Summarizing, the specimen shows:

1. A universal pericarditis externa.
2. An extensive adherence of the visceral to the parietal pericardium.
3. The presence of an old suppurative pericarditis with marked calcification and some ossification occurring chiefly in the atrio-ventricular region.
4. A tricuspid and mitral stenosis—an aortic stenosis and insufficiency.
5. Myocardial hypertrophy and dilatation.
6. A negative bacteriological study.

From the clinical and pathological findings in this case it seems fair to conclude, although this cannot be proved, that this man had, in the course of his ten years' illness, (1) an acute rheumatic fever, (2) rheumatic endocarditis resulting in his valvular defects, and (3) a complicating suppurative pericarditis with subsequent calcification and ossification, the exact etiological agent of the pericarditis being unknown.

On account of the rarity of such calcification and ossification and the unusual nature of the specimen it seems worth while to attempt to summarize briefly the available literature on the subject. Fritz Diemer in the *Zeitschrift für Heilkunde* first drew attention to this condition, describing in 1899 ten cases. In 1901 A. E. Jones in the *Transactions of the Pathological Society of London* collected and analyzed fifty-eight cases occurring in the literature from 1726 to 1897. In 1902 H. I. Wells reported four cases from Cook County Hospital. Simmonds of Hamburg reported in 1908 the X-ray diagnosis of such cases during life, and

in 1918 his assistant, E. F. Müller, added eight cases with a splendid critical discussion. These are the outstanding papers on the subject. The following points in these papers are of interest.

It is a very rare disease. Up to the present there are only seventy-five cases on record. It occurs three times more frequently in men than in women, and the age varies from twenty-nine to sixty-six years. The etiological agent in some cases was definitely the tubercle bacillus, in one case the anhemolytic streptococcus and, in another, old hemorrhage; occasionally a preceding rheumatic fever or pericarditis is mentioned. In fully two-thirds of the cases, however, the cause was not demonstrable.

The pathogenesis in these cases is not entirely clear. As you know, the course of a pericarditis is determined by the virulence and character of the infecting agent, the resistance of the individual, and the therapy applied. Depending on these factors one will find the outcome to be either (1) death of the patient or (2) complete restoration to normal or (3) more or less thickening of the pericardium or (4) adhesions—complete or incomplete—internal, external, or both, or (5) inspissated pus or blood or caseous masses—loculated or not. It is chiefly in such purulent, hemorrhagic, or caseous areas that lime deposition occurs. It occurs also occasionally in large areas of scar tissue or adhesions. Although the exact physico-chemical factors involved in calcification are not yet completely known, it is a general rule that wherever there are large areas of dead, dying, or hyalinized tissue, lime salts may be deposited.

One finds the following pathological features in these cases: (1) frequently a pericarditis externa, (2) an adherent pericardium—usually universal, and (3) calcification. This calcification is variously described in the form of granules or masses; plates in or between the visceral and parietal pericardium; irregular pieces extending into the myocardium; rings or bands (especially in the atrio-ventricular grooves), and rarely there is a complete enclosure or the so-called “cuirassed heart sometimes designated as the marble heart.” A few cases are described where the calcification proceeds outward from the bases of the valves. Very rarely, as

in the case reported here, a partial ossification in the calcific areas may occur. The other organs often show changes. The heart may be hypertrophied and dilated—pleural adhesions are frequent and cirrhosis of the liver is mentioned in one-seventh of the cases.

Müller brings out the following points in the study of his eight cases: (1) The process nearly always commences in the pericardium over the right ventricle. (2) It is progressive. (3) It later extends to the left heart. (4) The cause is subacute and acts for a long period of time. (5) The tubercle bacillus and the anhemolytic streptococcus could act in such a manner, he supposes.

There is no definite clinical picture of this disease. In 25 per cent. of the cases there were no symptoms and in the others merely those of cardiac insufficiency. Although metallic murmurs and os-teal percussion notes have been described, these seem to have been post-mortem retrospects. In 1908, Simmonds at Hamburg made the important observation that extensive calcification of valves, myocardium, or pericardium could be diagnosed during life by the X-ray. Since then Groedel, Schwartz, Weill, and Rieder have reported cases so diagnosed. Obviously, however, the diagnosis is only of importance in regard to the prognosis, since treatment is of no avail.

Discussion:

DR. ST. GEORGE: We had a case of calcification of the pericardium recently in Bellevue following an empyema which the patient had, and was operated for. The calcium deposited in the pericardium was torn during the attempted operative removal in such a way that it ruptured into the auricle and the patient bled to death. In this case the individual had no lesion anywhere in the endocardium. All the valves were normal. He had an adhesive pericarditis with this calcification which involved the pericardium on the side in which the empyema was, and also along the diaphragmatic surface.

There was no evidence of bone formation in this calcium.

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1. MULTILOCULAR ECHINOCOCCUS OF THE LIVER
2. HYDATID ECHINOCOCCUS OF THE SPLEEN

LEO EDELMAN, M.D.

(From the Pathological Laboratory of the Mount Sinai Hospital, New York)

The specimens which I have to present before the Society illustrate the two types of echinococcus found in man,—one, a multilocular or alveolar echinococcus of the liver and the other, shown mainly by way of contrast, a hydatid echinococcus of the spleen.

The first specimen was removed from a Russian woman, age 33, admitted to the surgical service of Dr. Berg, May, 1918. She entered the hospital complaining of pain, tenderness and discomfort in the right upper abdomen which had been present for about two months. There was no radiation of pain and no jaundice. In her past history she related that a mass was felt in that region by her family physician some two years before onset of symptoms but she declined operation at that time. This mass grew very slowly and only became tender a few weeks prior to admission to the hospital. On physical examination the patient appeared slightly emaciated, and presented a palpable mass just below the costal margin in the right upper abdomen which felt firm, nodular, and was freely movable with respiration, apparently attached to the liver. The blood picture and blood Wassermann were negative, as was the X-ray.

The patient was operated upon by Dr. Berg, who found a hard nodular mass intimately connected with the liver and overlying an apparently normal gallbladder. In the absence of any palpable metastases, he considered the condition a primary operable carcinoma of the liver and resected the tumor.

The excised specimen which was sent to the laboratory consisted of an irregular yellowish white, rather firm, nodular tumor mass measuring about 10 x 8 cm., roughly triangular on cross section with normal liver tissue at the base of the triangle. To the outer aspect of the mass, attached partly to it and partly to the liver tissue, was an apparently normal gallbladder. The cross section through the tumor presented a honeycomb appearance, the spaces containing cholesterolin-like material with granular detritus simulating necrosis. The gross appearance of the tumor suggested the following possibilities: (a) Gumma of the liver; (b) Colloid carcinoma with ulceration and necrosis; (c) Multilocular echinococcus.

Under the microscope the diagnosis of multilocular echinococcus disease of the liver was established, although no hooklets were found. The stroma defining the characteristic alveolar spaces consists mainly of sclerosed connective tissue derived from the liver, granular detritus with remnants of de-

generated liver cells, leucocytic infiltration (round cell and polymorphonuclear) near the periphery, and alveoli containing greatly contorted and folded chitinous vesicles filled with plugs of colloid material. Some areas show caseation and coagulation necrosis resembling a gumma or solitary tubercle with perivascular infiltration.

The patient made an uneventful post-operative recovery and was lost track of after leaving the hospital.

The second specimen was removed from a young woman, age 26, a native of Poland, admitted to the surgical service of Dr. Elsberg, September, 1921. She entered the hospital complaining of discomfort in her left upper abdomen which had existed for about ten days. Nothing abnormal was detected by her family physician prior to this time. Her previous history was negative. On physical examination the patient appeared moderately well developed and presented a rather firm fixed mass in the left upper abdomen, which reached downward to the level of the umbilicus and across to the mid-line. The liver was not palpable. There was no jaundice. The blood picture and blood Wassermann were negative. The temperature was normal, and urine negative. X-ray of pneumoperitoneum (Oxygen) showed an enlarged spleen and small liver.

The patient was operated upon by Dr. Wilensky, who found the spleen to be the seat of a tense cyst, rather firmly fixed to the diaphragm, and which he removed after considerable difficulty. The liver was explored and found to contain a smaller cyst in the right lobe. This was left intact for a subsequent removal.

The specimen which was sent to the laboratory consisted of a spleen somewhat elliptical and rounded, about the size of a large grapefruit, almost entirely replaced by a cyst, leaving only a thin shell of splenic tissue. The cyst proper was of the typical hydatid variety, having a white chitinous thick-walled membrane, smooth on its outer aspect, and a yellowish jelly-like substance loosely attached to its inner surface. The latter was found laden with numerous scolices and hooklets. The fluid contained within the cyst had a limpid opalescent appearance.

The microscopic section shows the characteristic lamellated structure of the cyst wall with areas of calcification.

There seems to be some doubt as to whether the two types of cysts presented are caused by the same species of *Tania*. The multilocular echinococcus was originally regarded as a colloid cancer until Virchow, in 1856, showed it to be parasitic in origin. His opinion held sway up to comparatively recent years. The Russian authority, Melinkow-Raswedenkow, working in a region where this type is almost endemic, bases his advocacy of a duality of species on various grounds, such as its peculiar growth and reproduction, its reaction to containing tissues and its somewhat

restricted geographical distribution. Mangold and Müller, as a result of feeding experiments, maintain that they obtained from it a different *Tænia*, evidenced by the appearance of the hooks and the distribution of the ova.

The cases of hydatid disease recorded in the United States were first collected by Osler (1882), Sommer (1895-96), Lyon (1902), and Magath (1902-1921). In all, there were 334 cases. Using the available data up to 1902, 91 per cent. occurred in foreign born, and 9 per cent. in natives. From 1902 to 1921 Magath found only four cases who were native born Americans and from the data he had at hand he could not conclude whether all or any of these patients travelled. Professor Osler refers to only six cases of multilocular disease of the liver reported in the United States, occurring chiefly in Germans. The specimen presented to this Society is the first that I could find in the records of Mount Sinai Hospital. The multilocular variety seems to be most prevalent in Russia including East Siberia, Bavaria, Würtemberg, the adjacent districts of Switzerland and the Tyrol, whereas the hydatid variety is most commonly found in Iceland, New Zealand, Australia, Argentina and Uruguay.

The parasite is most commonly located in the liver. Vegas and Cranwell in their review of 2,027 cases of hydatid cysts arrived at the following percentages: liver (74.9 per cent.), lung (8.5 per cent.), muscle (5.7 per cent.), spleen (2.3 per cent.), kidneys (2.1 per cent.), brain (1.4 per cent.), bone (0.9 per cent.), and various other organs (4.2 per cent.). Just how the larva enters the organ it infects is not clear. However, it seems that the larva hatches in the intestine, enters the blood stream, and stops in the organ where it happens to be arrested. The frequency of liver infection also points to a possible migration by way of the common bile duct.

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TERATOID CYST OF THE HYPOPHYSIS

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Among the cystic tumors found at the base of the brain there is a small group of cysts which are characterized by an inner lining of stratified squamous epithelium, and in which epithelial pearl-like structures, cholesterin crystals and occasionally bone are found. Through their attachment to some part of the pituitary body and because of their pressure upon the latter and the adjacent hypothalamic region, they frequently give rise to symptoms of pituitary disfunction and thus acquire in addition to histological interest a clinical significance.

Such tumors were often described as cholesteatomas, dermoids, epidermoids, and, because of occasional occurrence of cartilage or bone in their walls, they were also occasionally grouped with the teratomas.

This confusion in the classification of such cysts of the brain and its meninges was in part due to the fact that various incidental findings were accepted as fundamental features determining the character of such neoplasms. Thus the finding of the cholesterin crystals in such cysts led Mueller¹ to name them cholesteatomas, while Virchow² rejected this term, considering the cholesterin crystals simply an expression of a degenerative process, and preferred the old term of "Tumeurs Perlées."

For some time there was lack of agreement as to the origin of such tumors. Thus, Virchow believed them to arise from the pial connective tissue and by the process of metaplasia to gain their final histological features. Bonorden³ thought that ectodermal

tissue at the time of its invagination and formation of the "Anlage" of the anterior lobe of the hypophysis was the source of origin of such neoplasms. Beneke,⁴ however, maintained that the so-called meningeal cholesteatomata took origin from the endothelial lining of the meninges. He based his claim on the fact that he was able to demonstrate by the use of silver stain a strong similarity between the epithelial cells lining the cyst cavity and endothelial cells. Later,⁵ however, he revised his opinion and had accepted in part the view that some of such cysts have an epidermal derivation, this being particularly true of those cysts which contain sebaceous glands and hair. Bostroem⁶ studying in greater detail meningeal and dural cholesteatomata came to definite conclusions as to the nature and origin of such cysts. He decided in favor of their epidermoid character. Erdheim⁸ followed him by directing attention to a limited group of cysts which presented certain features in common, namely that they are always found at the base of the brain, in intimate connection with the pituitary body, are lined by stratified squamous epithelium and frequently contain cholesterol crystals. He traced the origin of such cysts to the embryonal rests of the subinvolved cranio-pharyngeal duct. The latter, which is the "Anlage" of the anterior lobe of the pituitary body, does not undergo complete involution, but leaves behind small groups of epithelial cells which can be normally found on the surface of the anterior lobe of the hypophysis. These cells often give rise to tumors of the character here described. Erdheim suggested the term hypophysial duct squamous-cyst-papillomata for such tumors and separated them from the epidermoid cysts of Bostroem by pointing out some differences in their gross anatomical relationships and histological features. The epidermoids of Bostroem being true derivatives of the skin give uniformly the kerato-hyaline granular reaction in the epithelial lining and often contain hair follicles and sebaceous glands. In the hypophysial duct tumor, no kerato-hyaline granules, no sebaceous glands and no hair follicles can be demonstrated. Then again, the hypophysial duct tumors are always found in the midline at the base of the brain, back of the optic chiasm in intimate

relation to the diencephalon, while the epidermoids of Bostroem may occur in any part of the brain and its meninges, and present no relation to the pituitary body.

Since Erdheim's publication of his work a number of hypophysial duct cystic tumors were reported.

D'Orsy Hecht⁹ described a so-called teratoma of the hypophysis in which he found bone and epithelial structures which he considered to have been derived from the anterior lobe of the hypophysis. It would seem that the failure to find any evidence of tissue derived from entoderm would not permit his case to be included with the teratomata as the latter are by definition trigeminal in origin.⁷

Jackson,¹⁰ Canavil and Jackson¹¹ and finally Duffy¹² described a number of similar tumors and have come to the conclusion that they were derived from the misplaced remnants of the ectoderm which was destined to form the anterior lobe of the hypophysis.

The case herewith reported is of interest because it presents features characteristic of the hypophysial duct neoplasms described by Erdheim. It also shows the presence of hair germs, kerato hyaline granules in the lining epithelium and sebaceous cells. Thus it appears to represent a neoplasm with structures common to both the hypophysial duct tumors of Erdheim and the epidermoid cysts of Bostroem. It would seem that there hardly can be a well-defined line of demarkation between these two groups of cysts, for apparently they have a common stem of origin.

Case L. P. No. 210957. The patient was a girl, six years of age, who had had no previous illness, and who had been quite normal up to the time of the onset of symptoms, six months before admission to the hospital. At that time she became markedly constipated; her sleep was disturbed; she became restless and lost her appetite and would experience constant thirst, demanding water very frequently. Several weeks later, on consulting a physician, the diagnosis of diabetes was made and the child was treated accordingly. With the increase of thirst and increase of water intake, there was too an increase in volume and frequency of urination. The child was losing strength, and would frequently complain of fatigue; she gave up playing, became irritable, and finally became confined to bed because of constant headaches and general weakness. A week before admission it was noted that the child's mouth was

drawn to one side, and her left shoulder drooped and would frequently twitch. She was admitted to the hospital with the complaint of headache, fatigue, excessive thirst, enuresis, loss of appetite and weakness of the left shoulder.

Physical examination showed a fairly well nourished child, somewhat undersized, with a profuse growth of lanugo hairs all over the body, presenting no evidence of acute illness or mental deterioration. There was ptosis of the right eyelid; external strabismus of the right eye due to weakness of the right internal rectus; the left pupil was larger than the right; both pupils reacted to light and accommodation. There was left facial weakness, and slight weakness of the left arm and hand; the latter was held in hemiplegic attitude. There was slight weakness of the left leg. The deep reflexes were more active on the left side, though generally reduced. There was a questionable Babinski, but gait and station were normal. The abdominal reflexes were not elicited. Spinal fluid was negative as regards cells and Wassermann. The diagnosis of neoplasm involving the posterior lobe of the pituitary and the right crus cerebri was made. The absence of distinct Babinski and the difference in abdominal reflexes indicated that the lesion was outside the substance of the peduncle.

Autopsy Findings.—(Examination of the brain only permitted.) On opening the cranial cavity the exposed dura was found to be normal in thickness and without demonstrable epidural or subdural hemorrhages. The underlying pia-arachnoid was markedly edematous and, because of the congestion of the arachnoid vessels, had acquired a purple hue. The cerebral hemispheres on the dorso-lateral surfaces showed evidence of increased intracranial pressure, the convolutions being definitely flattened and compressed. On raising the orbital surfaces of the frontal lobes, in the course of the removal of the brain from the cranial cavity, a large purple fluctuating mass presented itself at the base of the brain. It covered the optic chiasm and was adherent to the latter. Posteriorly it filled up the entire interpeduncular space. Its bulging inferior surface, which was partially free, was prolonged into a funnel-shaped process which seemed to be continuous with the pituitary body. The latter was extremely small in size, compressed, and was lodged in a shallow and eroded sella turcica. The base of the superior surface of this mass was firmly implanted in the substance of the basal surface of the brain. It occupied the entire intra-peduncular space, and because of pressure on the adjacent structures, the optic chiasm and tracts were flattened.

The tuber cinereum and the mammillary bodies could not be identified since the floor of the third ventricle was stretched and flattened by the tumor mass which almost obliterated the cavity of the third ventricle by its protrusion into it. The cerebral peduncles were displaced laterally and due to pressure were reduced in size; this was particularly pronounced on the right side. During the process of detachment of the brain from the base of the skull, the neoplasm was punctured and a dark-brown, granular, semi-fluid mass was found escaping from the cavity of the neoplasm. On opening the latter more fully, it collapsed and it was then noted that it was a rather thin-walled cyst, lined by a corrugated membrane which was beset irregularly by numerous small, glistening elevations. Cholesterin crystals were demonstrated in the

contents of the cyst by the employment of specific tests. The cyst measured about four centimeters in long diameter and about three and a half centimeters in width. By its expansion and central location it had stretched markedly the vessels constituting the circle of Willis, particularly the posterior communicating and anterior cerebral vessels.

Of the cranial nerves, besides the second, the third nerve on the right side was also compressed and flattened by the neoplasm. A horizontal, longitudinal section of the brain gave a still better view of the gross structural changes that were brought about by the neoplasm. The displacement and compression of the cerebral peduncle were brought well into view and the protrusion of a cyst into the third ventricle, practically obliterating the structures on the floor, was well shown. The cavity of the cyst was fully exposed and its inner wall was disclosed. The lining of the cyst gave the appearance of a mucous coat. At the left of the anterior portion of the cyst the wall was thickening, giving rise to a tuberos elevation, cartilaginous in consistency, and somewhat translucent in appearance.

Microscopic Anatomy.—In general the wall of the cyst was for the most part uniform in thickness and showed also a more or less uniform histological structure. It was composed of three layers. The innermost coat, a layer of stratified squamous epithelium, showed at a few points some little variation in the character and maturity of its epithelium. The middle layer consisted of loose connective tissue in which were imbedded numerous glandular acini and many small ducts. The glands were strongly suggestive of being salivary in character and the ducts were lined by tall cuboidal epithelium. The lumen of these ducts was filled with a pink staining colloidal substance. The third and outermost layer was composed of a fairly thin stratum of dense fibrous connective tissue, forming a boundary between the brain tissue and the cyst as well as the outer protective wall of the exposed part of the cyst.

A careful study of this lining epithelium showed its strong resemblance to the epithelium of the dermis of a young embryo. It consists of three layers, the outer corresponding to the epitrichium, the middle intermedian layer and the lowermost, the stratum germinativum. Here and there larger collections of cells composed mainly of the germinal layer gave the appearance of hair anlagen, or hair germs. Another feature of interest was the accumulation of deeply staining epithelial cells arranged in concentric layers, giving rise to structures not unlike epithelial pearls. The cells in the center of these pearls appeared to undergo degeneration, the peripheral cells having retained the structure of basal-cell epithelium and showed, when stained specifically, the characteristic intercellular bridges; when stained with Weigert's method, a blue color was imparted to these cells giving evidence of the presence of keratohyaline. These collections of epithelial cells were on the free surface of the cyst, and were responsible for the small elevations that have been noted on gross examination of the tumor.

In the small cartilaginous mass in the wall of the cysts there were found several types of embryonic tissues of mesodermal origin such as embryonal cartilage, mucous connective tissue, young fibrous tissue, newly formed bone with typical bone corpuscles, calcified trabeculae, endosteum and periosteum

crowded with numerous osteoclasts, osteoblasts, osteophytes, and marrow cells, filled with yellow granules which on staining with specific methods gave a typical iron reaction. In addition to these structures, there was a collection of cells arranged in long cords and supported by a fine reticulum of connective tissue. The cytoplasm of these cells was reticular in structure with the fat apparently washed out. In frozen sections, stained by specific fat stains, the cells appeared filled with large fat globules. The pycnotic character of the nuclei and the irregularity in the fat globules gave them the character of cells in sebaceous glands.

SUMMARY OF THE ANATOMICAL FINDINGS IN THE TUMOR DESCRIBED

The tumor was centrally situated, of the type of unilocular cyst, and was filled with dark-brown, coarse, granular material in which cholesterol crystals were found. Its interior was lined by corrugated mucous membrane on the surface of which were yellowish glistening papillary elevations. It bore a very intimate relationship to the hypophysis, being apparently attached to the infundibular process. Microscopically, it presented the following important features: It had a stratified squamous epithelial lining, which was embryonal in character. Here and there on the surface of the epithelial lining there was a heaping-up of cells which had a concentric lamellated arrangement, giving it the appearance of epithelial pearls. The latter were in various phases of degeneration, showing central areas of calcification, and were frequently surrounded by foreign-body giant cells. Alternating with these epithelial pearls, there were also found hair germs. Beneath this epithelial lining there was a connective tissue stroma, in which glandular tissue, salivary in character and in other places sebaceous in character, were found.

This tumor also contained embryonal cartilage, embryonal fibrous tissue, embryonic mucous connective tissue, and finally bone. The bone showed the characteristics of well-formed bone with its periosteum, endosteum, marrow cells, osteoclasts, osteoblasts, etc. It is quite conceivable in spite of all the earmarks of newly formed bone derived from misplaced bone "Anlage" that this tissue has developed by metaplasia through the degenerative process in the epithelial pearls, but it is unreasonable to

believe that the cartilage tissue, the mucous embryonic tissue, the salivary gland alveoli and sebaceous cells were all and each an expression of a degenerative process. It is most probable that they were elements derived from the two germ layers, ectoderm and mesoderm, which go to make up the mature skin. Thus we may assume that we are dealing here with an autochthonous teratoid growth derived from the elements concerned in the formation of the skin and that a misplacement of such cells from the two germ layers during the period of the invagination of the ectoderm in the course of the development of the hypophysis has laid the basis for the formation of the above-described tumor.

The failure to find hair follicles or sebaceous glands in the tumors described by Erdheim as hypophysial duct tumors is, perhaps, to be ascribed to the fact that such structures have escaped recognition because of their early embryonic character.

It is also evident from the reported findings by Duffy the presence or absence of kerato-hyaline granules cannot be looked upon as an important point of differentiation between epidermoids and cysts derived from hypophysial duct, as frequently poor and prolonged fixation may interfere with the kerato-hyaline reaction.

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A CONTRIBUTION TO THE PATHOLOGY OF SUB-
ACUTE EPIDEMIC ENCEPHALITIS

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In the literature we find abundant and accurate descriptions of the neuropathological findings in acute epidemic ("lethargic") encephalitis. Following the lead of Von Economo¹ a large number of investigators—Marinesco,² Bassoe and Hassin,³ Wegeforth and Ayer,⁴ Neal,⁵ and others—have recorded their observations on the gross and microscopic changes in the central nervous system caused by this disease. In their accounts of the lesions found in acute epidemic encephalitis, they refer generally to anatomical changes common to and characteristic of the acute form of the disease which are universally expressed in terms of perivascular infiltrations, a moderate amount of neuronophagia, a mild degree of glia proliferation, and occasionally hemorrhagic foci. It is further emphasized by them that the above changes are most commonly and most constantly found in the region of the midbrain and basal ganglia, not, however, to the complete exclusion of lesions in other parts of the central nervous system. Thus, lesions in the cerebral cortex (Hassin),⁶ spinal cord (Calhoun),⁷ and peripheral nerves (Burrows)⁸ have been described as occurring in acute epidemic encephalitis.

However, it is quite evident that, in spite of their abundance, the above-quoted observations do not exhaust the subject of the histopathology of acute epidemic encephalitis.

Von Economo⁹ has already reported a case which he called "chronic intermittently progressive lethargic encephalitis." His patient insidiously developed an atypical form of lethargic encephalitis which was characterized by alternate episodes of delirium and lethargy, dysarthria and slight pyramidal tract involvement. This condition remained unchanged for two months, and was followed by partial improvement. Later in the course of the

disease there developed dysphagia, paresis of the tongue leading to gradual debility of the patient and terminating in death a year and a half after the time of the onset of the disease.

Von Economo concluded that his patient was suffering from a chronic epidemic encephalitic process, to which new features were added in the terminal stage of the disease.

The anatomical changes which were associated with the lesions incurred during the early, acute period of the disease were (*a*) areas of softening with or without accumulations of granular cells; (*b*) bands of dense glia fibers; (*c*) small collections of glia cells, apparently cells which were at one time concerned with the process of neuronophagia; and finally (*d*) mild degenerative changes in the axis cylinders of long projection tracts. Among the new features he emphasizes recent perivascular hemorrhages, degenerative changes in ganglion cells, and perivascular infiltrations. He suggested that the recrudescence of the disease was probably due to incomplete elimination of the virus during the early period of the disease, and that a highly suggestive analogy was thus established between chronic progressive muscular atrophy in its relation to acute anterior poliomyelitis and this chronic form of lethargic encephalitis in its relation to acute epidemic encephalitis. It would appear from the clinical history of von Economo's case that an attempt towards healing must have occurred in the course of the disease, and it was apparently his aim to demonstrate this fact, but his histological descriptions fail to show any reparative change in the brain—the lesions described such as softening, accumulation of granular cells and extravasations pointing mainly to a lesion of destructive character.

In this regard, the findings in the group of cases reported in this paper demonstrate an important departure from the observations of von Economo, for we are in a position to demonstrate changes in the central nervous system that mark a well-defined tendency toward repair.

This series of cases might clinically be grouped with the mild protracted forms of lethargic encephalitis and could be termed subacute epidemic encephalitis. Early in their course they showed

a well-defined tendency toward recovery, then remained stationary for a variable length of time, finally to suffer a new insult leading into the acute, rapidly fatal, virulent form of the disease.

The important feature of this group of cases is the changes found occurring in the small cerebral vessels, indicative of an attempt on the part of the vascular system to repair the damage which occurred during the acute stage. The exacerbation of the disease, however, damaged the blood vessels, arrested the progress of repair, and this phase of the healing process became fixed.

Clinical Observations: It is not our aim to give a detailed account of the various clinical manifestations which have been observed in each of the four cases studied. A summary of the more constant and outstanding features common to all members of this group will be given. All of the patients studied have given a history of having had at one time a mild form of influenza in the course of the year preceding the onset of the apparently acute symptoms. They were admitted to the hospital complaining of general weakness, a variable amount of paresis and mild ocular symptoms. The clinical course during their residence in the hospital was marked at first by a tendency toward recovery, and improvement in their subjective and objective symptoms. This improvement, however, did not progress very far, and the condition became stationary. It is during this period that there occurred a sudden change; the patient became suddenly acutely ill, giving evidence of marked dyspnea, complete ocular palsies, dysphagia, and dysarthria. This apparently was the fatal turning in the course of events, as death took place soon after the onset of the acute recrudescence of the disease.

These striking features in the clinical course were paralleled by the anatomical changes to be described. It will be seen that lesions expressive of the three phases above noted in the clinical course of the disease can be demonstrated in the pathological material studied. Thus we shall find changes which are indicative of the early mild stage alongside of lesions suggestive of the reparative tendencies, and finally areas of destructive processes mark the final acute and fatal outcome of the disease.

Autopsy Findings: The gross anatomical changes consisted mainly of extreme congestion of the pial vessels, particularly over the ventral surface of the medulla and pons. No definite meningeal hemorrhages were noted in any of the four cases. Small petechial hemorrhagic foci, however, were seen on sectioning of the brains. The larger vessels at the base were followed out in their course to the smaller branches, and no arteriosclerotic changes could be found. The consistency and topography of the brains examined showed no abnormalities of note.

Microscopic Findings: In the course of the histological studies, a thorough search was made for minute anatomical changes throughout the brain stem, cerebral and cerebellar cortex. Particular care was exercised in the examination of the sections from the mid brain, basal ganglia and medulla, as the more important changes were anticipated there.

In general, it may be said, and this is highly significant, that lesions typical of the acute form of epidemic encephalitis were not conspicuous; nevertheless, in the vicinity of the aqueduct of Sylvius and in the medulla vessels were found showing the typical small round cell, adventitial infiltration. The most frequent findings throughout the brain stem were numerous perivascular and extravascular hemorrhages. That these hemorrhages were not agonal was shown by the presence of blood pigment in the adventitial spaces of blood vessels in parts remote from the seat of the extravasation of blood. Wherever such hemorrhages have occurred the walls of vessels involved showed no thickening or perivascular infiltration. Apparently these vessels were spared in the first attack of the disease and during the exacerbation of the disease the adventitia of these vessels was damaged to such an extent that it was incapable of proliferative changes and could not withstand the pressure of vascular engorgement. These hemorrhages were most extensive and most frequent in the medulla, this being noteworthy in its bearing on the clinical course of the disease. Another frequent finding was the small

accumulations of glia cells in groups of five or eight cells about ganglion cells undergoing neuronophagia.

Further evidence of an extensive degenerative process in the brain was found in the wide distribution of fat granules and globules in the cells of the adventitial coat of the vessels throughout the brain stem, and to a slight degree in other parts of the central nervous system.

Glia changes were also expressed as mild forms of proliferation and mobilization about blood vessels, in the subependymal layer in the floor of the fourth ventricle and of the aqueduct of Sylvius, and in the accumulations already described above. Only arterioles and capillaries were apparently singled out by the glia cells in their proliferative aggregation, and this fact coupled with adventitial changes in the smaller vessels constitute the most important pathological changes observed.

It was already pointed out that only close scrutiny yielded here and there a vessel with typical perivascular infiltration amid widespread perivascular and extravascular hemorrhages, while organization in the adventitial coat of the smaller vessels and capillaries was the most obvious and generalized change in the structure of the involved areas of the brain stem.

Apparently the perivascular, lymphocytic infiltration, which is the early anatomical manifestation of the disease, here gave place, through the proliferation and metamorphosis of lymphocytic elements and adventitial cells, to fibroblasts which thickened considerably the walls of the vessels. Further advance toward a distinct periarteritis was made through the progress of the same process of metamorphosis of the elements of perivascular infiltration. This is apparent in the thickening of the adventitia which is extremely rich in fibrous elements, though numerous lymphocytes are still found in the fibrous meshwork.

More striking, however, are the changes in the small capillaries of the involved areas, particularly in the gray substance about the aqueduct of Sylvius. They are expressed in the swelling and proliferation of the adventitial cells and the swelling of the intimal endothelial cells. This feature was often so pro-

nounced as to obliterate almost completely the lumen of the vessel.

Small vessels which are only moderately thickened were seen frequently surrounded by glia cells, a few lymphocytes and an occasional granular cell.

Microscopic examination of the vessels aided by specific stains such as resorcin-fuchsin, Van Gieson and Sudan III disclosed no features pointing to arteriosclerosis. Elastic membranes were intact; there was no splitting of the latter, no deposits of hyalinizing plaques and no calcification in the intima or media.

The pia-arachnoid appeared normal except in a few small areas where it was distinctly thickened and presented features of organization such as the presence of many fibroblasts, small, newly formed blood vessels and lymphocytes.

Significance of the Histological Changes: It is evident that the modification of the structure of the small vessels forms the essential pathologic change. We believe that the primary attack of the virus is upon the wall of the small and medium-sized vessels, and that the vessel wall is affected by the virus in a manner proportionate to its virulence.

It is our opinion that many of the elements of the perivascular infiltration have their ultimate origin in the Virchow-Robin's space—cells often referred to by other writers as endothelial cells. These cells, characterized by a large amount of cytoplasm and clear vesicular nuclei, were found to be the predominating element in our preparations, and were frequently found in various stages of cell division.

It appears to us, then, that production of elements of infiltration, destined perhaps to repair damage occurring in the immediate vicinity of the vessel, is an important function of the adventitia. Thus, when the virus or even a mineral poison reaches the adventitia, it reacts by formation of adventitial elements, provided that the vessel wall is not damaged to an extent of losing its potency for adventitial proliferation. Should the virus or toxin, however, be so destructive to the vessel wall as to in-

capacitate it for cell proliferation and weaken it so it could not withstand the pressure of vascular engorgement, then perivascular hemorrhages will occur in large numbers, a feature characteristic of the acute, virulent type of the disease.

The reverse is also true, for when the virus reaches the vessel in a small amount or in attenuated form, changes pointing to subacute lesions follow, as was shown in our case.

Such interpretation of the histologic changes in the brain led us to suggest the grouping of acute epidemic encephalitis into:

1. An acute infiltrative form, with the dominant feature of perivascular infiltration.

2. An acute hemorrhagic form, where the virulence of the disease is expressed in numerous extensive hemorrhages.

3. A subacute productive form, as described in this paper.

The acute infiltrative is the early stage of any acute form of acute epidemic encephalitis which may resolve itself rapidly into the fatal hemorrhagic type or the protracted, mild productive form.

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DR. DOUGLAS SYMMERS, President.

EXPERIMENTAL RICKETS IN RATS

(Studies from the Department of Pathology, College of Physicians and Surgeons, Columbia University, New York)

Introduction: Since the fall of 1920, a group of workers in the Department of Pathology at Columbia, aided by a grant from the Commonwealth Fund, has been engaged upon a study of experimentally produced rickets in rats.* As you are aware, similar researches are being carried out at Baltimore and New Haven by McCollum, Shipley, Park and their associates, and more recently investigations along similar lines have been begun by McClendon and Baugness¹ at the University of Minnesota, and by Korenschevsky² at the Lister Institute.

Our own work has developed upon the basis of a chance observation.³ Professor H. C. Sherman, of the Department of Chemistry, had for a number of years been interested in the mineral metabolism of rats, and at our request, very kindly sent to us for examination some of the animals which had died during his experiments. Of these rats, some proved to be rachitic, others showed normal or merely osteoporotic bones; and on subsequent inquiry, it was discovered that the determining factor was the absence or presence of basic potassium phosphate in the diet. Here, then, was a simple and, as it proved, unfailingly reliable method for producing and preventing rickets under controlled experimental conditions.

Further work has followed logically and obviously enough from this basic observation. We have varied and modified the inorganic and organic constituents of this rickets-producing diet, so as to define as precisely as possible the essential and important factors in the production or prevention of the disease in rats.

* The organization of the work has been as follows: Director: Prof. J. W. Jobling. Chemistry: T. F. Zucker and M. Gutman. Diets and Care of Animals: G. F. McCann and M. Barnett. Experiments on Light and Fat-Soluble Vitamines: A. F. Hess, L. J. Unger, and M. Weinstock. Pathology: A. M. Pappenheimer. Radiography: Dr. Steiner and Miss Shaw. Technician: I. B. Tice, Jr. The following students have taken an active part in the experimental work: Mrs. Angus M. Frantz, Misses Stimson, Strauss, Stanley-Brown, Lichtenstein, Mrs. Silverberg, Messrs. Klein and Seidlin.

Other problems which have been taken up are the rôle of the fat-soluble vitamine A, the behavior of the inorganic blood phosphate on various experimental diets, and the effects of light and other forms of radiant energy, in the prevention of the experimental disease. A study of the curative principles of cod liver oil is also being carried out, and will be reported upon elsewhere.

By way of introduction to a more detailed presentation of these experiments, we may describe briefly the type of bone lesions seen on the typical diets; and it may be of interest also to trace the process of healing under the influence of cod liver oil. The ribs have been chiefly studied. The large number of animals used (over 800) has made a study of the long bones impracticable, but whenever this has been done, the changes in the ribs have been found to be a reliable criterion of the lesions in other bones.*

PATHOLOGY

High Calcium-Low Phosphate Diet (Diet 84): On this diet, histological changes identical in all details with those of human rickets have been invariably found. The lesions may be summarized as follows:

Resting cartilage—unchanged. Zone of preparatory calcification greatly increased. Normally this is composed of not more than five to six cells; in the rachitic animals on this diet, it may be 50 cells or more in depth. The cartilage is continued in the form of irregular prolongations into the diaphysis. The matrix is wholly calcium-free, except for the extreme tips of the prolongations. Osteoid is present in great excess both at the metaphysis and on the periosteal and endosteal surfaces of the cortex, where it may lead to great reduction in the size of the marrow cavity. Infractures, with large masses of calcium-free cartilaginous and osteoid callus, are of frequent occurrence. The calcified cortex is reduced in width and in places interrupted. There is often great angular deformity and swelling at the chondro-costal junction. (Fig. 2.)

* The bones were decalcified for 5 days in Mueller's fluid, stained with hematoxylin-eosin, and silver nitrate-safranin. The progress of the bone lesions in each case has been followed by radiographs.

High Calcium, and Phosphate Adequate for Bone Growth
(Diet 85): On this diet, deficient in the character of the pro-

FIG. 1. Rat 38. Full diet. Normal rib. Zone of preparatory calcification (*p*) does not exceed three cells in depth. Matrix calcified. Trabeculae of spongiosa (*s*) show orderly parallel arrangement. No osteoid margin is visible.

teins, in the fat-soluble vitamins, and in its mineral constituents, other than Ca and PO_4 , growth is unsatisfactory. Examination of the bones shows no rachitic changes, but there is simple osteoporosis without rickets. The zone of preparatory calcification is reduced to three or four cells, the matrix is completely calcified. Endochondral osteogenesis is imperfect, the trabeculae of the primary spongiosa being sparse and poorly formed. The bony cortex is thin, and the marrow cavity wide. There is no excess of osteoid, and an osteoid border is rarely seen about trabeculae or cortex.

High Phosphorus-Low Calcium Diet (Diet 85-C): This diet, as has been pointed out also by the Johns Hopkins workers,⁶ leads to an atypical form of rickets. The following features differentiate this type of bone changes from that produced by a high

FIG. 2 Rat 246. 34 days on Diet 84 (high calcium-low phosphorus). Advanced typical rickets. Zone of preparatory calcification very deep and irregular, entirely Ca-free (*p*), except at extreme tip (*ca*). Great excess of subchondral and cortical osteoid (*o*). Calcified cortex reduced in width (*co*).

calcium-low phosphorus diet. The zone of preparatory calcification is but slightly greater than in normal ribs, and in some cases does not exceed 5 or 6 cells. The calcium depositions in the matrix are more abundant than on Diet 84, though usually limited to the distal portion of the cartilage. In the subchondral zone, which unlike the typical rachitic metaphysis is free from

metaplastic cartilage, are broad trabeculae, composed almost wholly of calcium-free osteoid. The cortical osteoid is moderately increased, and infractions are present. The calcified cortex is reduced in width, and is more readily decalcified than in diets containing an adequate amount of calcium. In general, there

FIG. 3. Rat 495. 39 days on Diet 85-C (low calcium-high phosphorus). Zone of preparatory calcification (*p*) 9 to 12 cells deep, fairly regular columnar alignment, calcium deposition limited to prolongations of matrix into spongiosa (*ca*). Spongiosa (*s*) composed of stout osteoid trabeculae extending only a short distance towards diaphysis. Cortical osteoid slightly increased. Marrow cavity wide. Note absence of marked swelling and deformity at chondro-costal junction.

is little swelling or deformity at the chondro-costal junction. (Fig. 3.)

Deficiency of Both Calcium and Phosphorus (Diet Q): This

diet only exceptionally leads to a simple osteoporosis, the conditions commonly found being intermediate between those of osteoporosis and rickets. In the radiograph, the defect at the upper extremity of the tibia is much narrower than in the typically rachitic rat, and the swelling and deformity are negligible. Infractions, however, do occur and the bones are delicate and fragile, rather than pliable.

Histologically, the zone of preparatory calcification is increased in depth, but not to the same degree as on Diet 84. Calcification of the matrix is either absent or limited to the distal portion and to the short prolongations into the diaphysis. There is moderate increase in the osteoid of the spongiosa and cortex—less extreme, however, than on Diet 84. No clear evidence of increased osteoclastic resorption was found. The detailed descriptions of the lesions obtained with other variously modified diets must be left for final publication.

Healing Under Influence of Cod Liver Oil: We owe to Shipley, Park, McCollum, and their co-workers,⁶ the demonstration that the rickets of rats, like that of human beings, is definitely benefited by the administration of cod liver oil. The deposition of calcium in the rachitic metaphysis of the tibia under treatment is so clearly evident in the radiograph that it affords a convenient and reliable biological test of the activity of this substance. Park has excellently described the histological changes in their earlier stages. We shall not take the time to cite his work in detail, but shall try to give a brief description of the healing process as we have observed it in our own animals. Our studies are still incomplete, but the material which has already accumulated is sufficient to give a fair idea of the main features which mark the restitution of the rachitic bone to an approximately normal condition under the influence of this agent.

On Diet 84, the cartilage throughout the zone of provisional calcification is virtually Ca-free. Rarely at the extreme tip of the irregular prolongations of the cartilage into the metaphysis, one may find a small amount of calcium. The first detectable effect of the administration of the cod liver oil, or one of its active fractions, is the deposition of calcium phosphate in this

zone of preparatory calcification. The exact site of its deposition varies somewhat, but it is apt to appear first in the lateral portions of the cartilage. Somewhat later, it may extend transversely across the cartilage as a broad band. Gradually the area of calcification extends, but two facts should be noted. First, the basal cells, which are apt to retain more or less of their columnar arrangement, have no calcium about them; and secondly, areas in which the cartilage appears to be necrotic also become calcified with difficulty.

The time relations vary with the dosage, and probably also with the severity of the rachitic lesions at the time when treatment is begun. We have observed a deposition of Ca in the cartilage within twenty-four hours after a single dose of five drops, and after five to seven days calcification is often present throughout the greater portion of the cartilage. The complicated rearrangements necessary to bring about a complete return to the normal require, however, a considerably longer period.

Accompanying this deposit of calcium in the matrix of the cartilage, there is a laying down of the salt also in the osteoid tissue. In the perichondral osteoid, which is always very considerably thickened, one finds a granular deposit beginning in that portion of the osteoid contiguous to the cartilage. The granules of calcium are ranged often in linear rows at right angles to the cartilage, like minute stalactites. In the trabeculæ of the spongiosa and in the osteoid masses, which envelop the calcified bone of the cortex, new calcium is deposited, at first in loose granular form, or as seen in hematoxylin-eosin preparations, as a faint purple cloud, fringing the originally calcified bone. As this osteoid tissue becomes transformed into fully calcified bone, the osteoblasts embedded in its substance change their character, becoming more angular, pyknotic, and acquiring the filamentous processes characteristic of adult bone corpuscles. The deposit of the calcium always begins in that portion of the osteoid which is adjacent to the originally calcified bone, so that one of the earliest and most characteristic indications of active calcification is the wiping out of the sharp line of demarcation between the calcified bone and the osteoid border.

The active deposition of calcium in the cartilage and osteoid is very easy to demonstrate and to understand, at least from the morphological point of view. But the return to the normal involves also a resorption of the excessive cartilage and osteoid tissue which make up the swollen rachitic metaphysis, and there are details in this process which are less easily analyzed.

The excess of cartilage appears to be disposed of in the following way. Following the calcification of the matrix, the cartilage cells are invaded on all sides by blood vessels and polygonal mononuclear cells in exactly the same fashion as takes place normally at the epiphyseal junction; the only difference being that this opening up of the cartilage cells is most irregular. With the disappearance of the cells, there remains for a time the calcified matrix, in the form of curved rods which are destined to form the scaffolding for new bony trabeculæ.

The removal of the excess cartilage, therefore, involves no new principles. It is apparently conditioned by the calcification of the matrix, just as in normal endochondral growth. The resorption of the osteoid tissue, which undoubtedly occurs also on a large scale, is less easy to follow. We have observed that at this stage, the osteoid tissue still present in the subchondral region stains less intensely, has a looser, more fibrillar texture, and often seems frayed-out at the margins as if it were undergoing solution. Occasional multinucleated cells may be found, but osteoclastic resorption seems to play a little part in the process. Possibly further study with differential stains will add details to our understanding of this process, but the interpretation of the finer changes underlying bone resorption has always been a matter of difficulty.

However brought about, this resorption of the excess of osteoid very clearly takes place first in the proximal half of the rachitic metaphysis,—that is, the portion nearest the cartilage, and only later affects also the distal portion. (Figs. 4, 5.)

Accompanying the removal of the excessive cartilage and osteoid there takes place also an extreme and striking distention of the blood sinuses. Whether or not we assign to the blood vessels an active rôle in the resorption of the cartilage and osteoid,

this extreme vascularity is certainly one of the most characteristic and striking features of the healing process. Some of our preparations show very clearly also the penetration of the cartilage with blood vessels, which grow in from the perichondrium, at a level just beyond that which will form the new epiphyseal line. Schmorl⁶ has shown that these endochondral blood channels anastomose with those in the subchondral zone, and that they play an important directive part in the healing process.

FIG. 4. Rat 549. 39 days on Diet 84. During the last ten days, received 1 drop of cod liver oil daily. Rib shows healing rickets. The zone of preparatory calcification is being reduced to average width of 10 cells (*p*), the prolongations of the cartilage show dense calcification of matrix (*ca*), and the cells are being invaded by wide blood sinuses (*v*). There is fresh Ca deposition in perichondral osteoid (*pc*). Much uncalcified osteoid is still present in the distal portion of the rachitic metaphysis (*o*).

We have not followed the healing process beyond this stage. It is clear, however, that the new epiphyseal line is reconstituted at the base of the cartilage by the resorption of the cartilaginous and osteoid metaphysis; and that this resorption is initiated by the deposit of calcium in the matrix of the cartilage, and to a lesser extent in the osteoid itself, and accompanied by great dilatation of blood vessels. The interesting problem of the mode of action

FIG. 5. Rat 474. 63 days on Diet 84. Treated 4 weeks with daily dose of 3 drops of cod liver oil. Rickets—late stage of healing. The zone of preparatory calcification is reduced to 6 cells or less, the matrix being calcified between the distal 2 or 3 cells. A few nests of cartilage cells still remain in the depths of the original metaphysis (*c*), the remainder having been resorbed. They are surrounded by densely calcified matrix. A new and very irregular spongiosa has been formed (*sp*); the trabeculae in the subchondral zone are completely ossified, but osteoid tissue is still found in the distal portion of the metaphysis (*o*). The blood sinuses are enormously dilated.

of this curative agent may thus be defined as follows: how does cod liver oil bring about this deposition of calcium in the cartilage and osteoid? The later phases of the healing processes, as we have seen, follow upon this preliminary calcification along the lines observed in normal bone formation. It is the initial step which requires explanation.

THE EFFECT OF VARYING THE INORGANIC CONSTITUENTS

The rickets-producing Diet 84, described by Sherman and Pappenheimer,³ has served for the basis of the following studies. Over 150 rats have been kept upon this diet for periods of three to five weeks, and in every case rickets has developed. The protective action of potassium phosphate has also been confirmed by the use of Diet 85. (See table.) More than 50 rats have

TABLE I

| <i>Diet 84</i> | | <i>Diet 85</i> | |
|-----------------------|-----|--|-----|
| Patent flour | 95. | Patent flour | 95. |
| Sodium chloride | 2.0 | Sodium chloride | 2.0 |
| Ferric citrate | 0.1 | Ferric citrate | 0.1 |
| Calcium lactate | 2.9 | Calcium lactate | 2.5 |
| | | Basic potassium phosphate (K_2HPO_4) | 0.4 |

now been given this diet and in no case has rickets developed.

Determination of the Rôle Played by Potassium and Phosphate Ions, Respectively in the Protection Given by Basic Potassium Phosphate: Secondary sodium phosphate in the proportion of 0.8 per cent. of the diet was substituted for the secondary potassium phosphate in Diet 85, this amount being calculated to contain an equivalent amount of phosphorus (.072 mgm.). Of four rats on this diet none developed rickets.

For another group of three rats 0.35 per cent. of potassium chloride was used, thus adding an equivalent amount of potassium to the diet in the form of chloride instead of phosphate. These rats all developed rickets in as severe a form as did control rats on Diet 84.

It is obvious that the protective effect of basic potassium phosphate is due to the phosphate and not the potassium ion.

Determination of the Amount of Phosphate Necessary to Protect

Rats were placed upon diets in which graded amounts of basic potassium phosphate had been substituted for equivalent amounts of calcium lactate in Diet 84. Additions of 10, 25, and 50 mgm. per cent. of phosphorus were made in this way. Of the three rats receiving 50 mgm. per cent. of added phosphorus, one showed no evidence of rickets. The other two showed slight or early lesions.

The rats receiving 10 and 25 mgm. per cent. of added phosphorus all showed definite rachitic lesions.

Since Diet 85 which contains 72 mgm. per cent. added phosphorus affords complete protection against the development of rickets, the protective level of phosphorus in this particular series of diets is seen to lie between 50 and 75 mgm. per cent. added to the original rickets-producing diet.

Modification of Inorganic Constituents other than Calcium and Phosphorus

Five rats were given a diet composed of flour and 5 per cent. of a salt mixture prepared similarly to that described by Osborne and Mendel except that no phosphoric acid was included. These rats all developed marked rickets.

This salt mixture as given contains an amount of calcium approximately equivalent to that in Diet 84, and it also contains sodium, potassium, magnesium, iron, iodine, fluorine, chlorine, manganese, and aluminium in the amounts considered necessary for adequate growth, with the single exception of phosphorus. The development of rickets in these rats would seem to indicate that these other elements have no protective action.

The sodium chloride content of Diet 84 is 2 per cent. In another experiment this was reduced to 0.5 per cent. Three rats on this diet developed typical rickets, showing that excess of sodium chloride is not a factor in the production of rickets by Diet 84.

Effect of a Deficiency of Ca in the Presence of an Excess of Phosphate

The diet used in this experiment, Diet 85-C, has the following composition:

| | Per cent. |
|---------------------------------------|-----------|
| Patent flour | 95.0 |
| Sodium chloride | 2.0 |
| K ₂ HPO ₄ | 2.9 |
| Ferric citrate | 0.1 |

Rats on this diet have all shown lesions which are considered to be those of an atypical rickets. These lesions have been discussed in the introductory portion of this paper.

Effect of a Deficiency of Both Ca and PO₄

The diet used for this study was composed of:

| | |
|-----------------------|------|
| Patent flour | 97.9 |
| Sodium chloride | 2.0 |
| Ferric citrate | 0.1 |

It is deficient in both Ca and phosphate, the calcium being estimated to be 0.018 mgm. per cent. as compared with 0.553 gms. per cent. in Diet 84. The P content is approximately .088 per cent. or five times that of the calcium. Of eleven rats on this diet, nine have shown lesions which are similar to those produced by the high phosphorus, low calcium diet described above, while the remainder have developed an osteoporotic condition of the bones.

Effect of Phosphate Deficiency upon the Bones of Adult Rats

Three rats after 126 to 182 days of normal growth upon normal diets were placed on Diet 84. One rat was kept on the deficient diet for ten days, the other two for forty-two days. They all showed practically identical lesions. The zone of preparatory calcification was very narrow. There was a definitely increased osteoid margin about the trabeculae of the spongiosa and along the endosteal surface of the cortex. This osteoid was

bordered by distinct osteoblasts. The calcification of the cartilage remained unimpaired.

MODIFICATIONS IN THE ORGANIC COMPONENTS

It seemed desirable to study the following questions:

1. Is phosphorus, ingested in organic combination, of equal value as compared with inorganic phosphorus, for the purposes of bone formation?
2. Do the water-soluble and fat-soluble vitamins exert any protective or curative effect, aside from the phosphorus content of the substances in which they occur?
3. Is it possible to produce rickets on a diet more nearly adequate for proper nutrition and growth than Diet 84?

Effect of Addition of Casein to Diet 84

In order to study the effect of phosphorus in the form of phospho-protein, three diets were used in which 5, 10, and 15 per cent. of casein was substituted for the same amounts of flour in Diet 84. The casein used was the ordinary commercial product which had been extracted with cold alcohol by slow percolation until the washings were colorless, and then extracted for forty-eight hours with two changes of ether. The diet containing 10 per cent. of casein has a P content of 162 mgm. per cent. or approximately that of Diet 85. The diet containing 15 per cent. of casein had a phosphorus content well in excess of the protective level found for diets containing inorganic phosphates.

Three rats were placed on each of the three diets. All nine showed signs of definite rickets in x-rays taken on the 22nd to 28th days. One rat on the 10 per cent. casein diet and one on the 15 per cent. diet killed at this time showed definite rickets, but in the former there were evidences of early healing.

The other four rats which were receiving these two diets showed complete or partial healing of the lesions at 35 to 37 days. The rats on the 5 per cent. casein diet, a diet well below the previously determined level of protection by the Na and K phosphate, all showed definite rickets after 28 days with no signs of healing.

From this it is concluded that the protection afforded by casein is not wholly equivalent to that given by the same amount of phosphorus in the form of basic potassium phosphate.

Effect of Addition of Lecithin

Three rats were given a diet similar to Diet 84, except that 2 per cent. of the flour was replaced by an equal weight of commercial lecithin. This amount of lecithin contained about 79 mgm. of phosphorus, the diet thus having a phosphorus content equal to that of Diet 85. The three rats showed no evidence of rickets either by x -ray or microscopically, showing that phosphorus in the form of lecithin afforded protection equal to that given by basic potassium phosphate.

Effect of the Addition of Yeast

Yeast extract (Harris Yeast Vitamin) was added to the diet with the double purpose of ascertaining the influence of the water-soluble vitamine and of another phosphorus-containing compound. Two groups of two rats each were given diets in which 0.5 per cent. and 1.25 per cent. of yeast extract replaced equal weights of flour in Diet 84. The 0.5 per cent. was calculated to give 25 mgm. of extract per day (each rat ate about 5 gm. of the total diet per day) and added 21 mgm. per cent. of phosphorus to the diet. 1.25 per cent. added 52 mgm. per cent. of phosphorus to the diet. Twenty mgm. per day of a similar yeast preparation were found by Osborne and Wakeman⁷ to carry sufficient water-soluble vitamine for the growth needs of young rats so that even the 0.5 per cent. vitamine extract diet was ample in this respect. All the rats on these diets developed marked rickets.

In a preliminary experiment a larger amount of yeast vitamin was given, approximately 100 mgm. per rat, each day. These rats failed to develop rickets, but here the phosphorus added to the diet was in excess of that which had been previously shown to prevent rickets.

Effect of Addition of Egg Albumin

The phosphorus-free protein, egg albumin, was added to the diet in an attempt to improve the nutrition of the animals. Ten per cent. was substituted for flour in Diet 84. Three rats showed marked rickets after 26 to 28 days on this diet, and this addition did not strikingly improve their nutrition.

The Addition of Butter and Butter-Fat

This was of especial interest in view of the questions in regard to the rôle of the fat-soluble vitamin in rickets. Mellanby's⁸ views and experiments in support of this idea are well known.

Subsequent work has, in general, been unfavorable to this conception, and various authors have failed to produce rickets by diets deficient in fat-soluble vitamin, in monkeys, infants, dogs, rats, kittens, guinea pigs, or pigs.

Shipley, Park, McCollum, and Simmonds⁹ cite experiments in which a diet adequate in phosphorus but deficient in fat-soluble vitamin failed to produce rickets.

Four rats were given Diet 84, modified by the substitution of 5 per cent. of pasteurized butter for flour. This amount of the same brand of butter completely protected all control animals against keratomalacia and evoked a characteristic rise in the weight curve with cure of keratomalacia in two rats which had been maintained for a long time on a fat-soluble vitamin-deficient diet. The rats on Diet 84 plus 5 per cent. butter all showed marked rickets after 32, 43, and 43, and 45 days.

To three other rats, 0.4 gm. of fresh butter (made in the laboratory from raw cream) was given daily. These also showed typical though moderate lesions when killed after 28 to 30 days on the diet.

Two rats, previously made rachitic, were transferred to a diet containing 10 per cent. of raw butter fat, and three similar rats to a diet containing 10 per cent. of pasteurized butter fat. After eight to ten days on these butter fat containing diets, these rats were killed. All showed marked rickets with no evidence of healing although the general health of these rats was excellent.

The foregoing experiments seem to us to show that the fat-soluble vitamin, although present in sufficient quantity to prevent the usually accepted signs of fat-soluble vitamin deficiency, neither prevents nor cures rat rickets.

Effect of Adding Meat to Diet 84. Meat and Flour Diet

Three rats were fed for periods of 33 to 39 days on Diet 84, supplemented by the addition of chopped and dried round steak *ad libitum*. The growth on this diet was normal, and the bones of these animals showed a normal structure. This diet was adequate in both calcium and phosphorus.

Three rats were placed for a period of 35 days upon a diet of dried chopped steak and flour without the addition of sodium chloride, ferric citrate or calcium lactate. This diet was rich in phosphorus, contributed by the meat, but deficient in calcium. These rats developed lesions very similar to those described above as occurring in the other rats on diets low in calcium, but rich in phosphorus—lesions which are considered to be those of an atypical rickets.

Amplified Rachitic Diet

The following diet has produced rickets in the entire series of seventeen rats on which it has been tried.

| | Per cent. |
|--------------------|-----------|
| Patent flour | 80.9 |
| Egg albumin | 10.0 |
| Butter-fat | 5.0 |
| Salt mixture | 4.1 |

The salt mixture furnishes the following constituents:

| | Gm. per 100 Gm. Diet |
|---------------------------------------|----------------------|
| KCl | .85 |
| Na ₂ CO ₃ | .85 |
| MgCO ₃ | .286 |
| Ca lactate | 2.00 |
| Ferric citrate | .1 |

On this diet approximately normal growth is obtained for periods of nearly a month. The addition of 72 mgm. of phos-

phorus in the form of basic potassium phosphate causes growth to be normal for periods of six weeks and longer. This latter diet has a P content of about 140 mgm. per cent. which has been shown to be about on the borderline of protection,—at least for all the diets of our experiments. As would be expected, then, some of the thirteen rats have developed rickets on this diet, while others have not, although the growth has, in almost every case, been excellent. In many cases, the rickets has been most severe in the rats which have grown most rapidly.

OBSERVATIONS ON THE INORGANIC PHOSPHATE OF BLOOD IN EXPERIMENTAL RICKETS IN RATS

The work of Howland and Kramer¹⁰ on the level of the inorganic phosphate in the blood in human rickets led to the conclusion that during the period of active rickets in children the inorganic phosphate of the blood is reduced, and that during the process of cure either by sunlight or cod liver oil, the phosphate rises again to its normal level.

Since the experimental rickets produced in rats is comparable in most important respects to human rickets, it was thought of interest to determine whether the same changes in blood phosphate could be demonstrated in rats. In applying the blood phosphate work of Howland and Kramer to experimental rat rickets, we have obtained results which on the whole agree very well with those reported by them at a recent meeting of the Society of Biological Chemists.

Because of the small quantities of blood which can be obtained from the animals, it seemed advisable to do the determinations on whole blood rather than plasma, if possible. Experiments undertaken to show the relative distribution of the inorganic phosphate in plasma and whole blood indicate that the level of phosphate is practically the same inside and outside the cells, and is maintained at a very constant level from day to day. Therefore, as far as inorganic phosphate is concerned, it is immaterial whether the determinations are done on whole blood or plasma.

TABLE II
Inorganic Blood Phosphate of Rats on Various Diets
 Mgms. P per 100 c.c. of blood

| No. | Diet | | No. of Rats | Determinations | Rickets | Blood Phosphate | | |
|--------------|--------|---------|-------------|----------------|--------------------------------|-----------------|------|-------|
| | Mgm. P | Mgm. Ca | | | | Max. | Min. | Aver. |
| Normal. | ? | ? | 55 | 43 | 95% show none | 8.2 | 5.1 | 6.2 |
| 84 | 86 | 550 | 40 | 18 | Marked in 100% | 4.9 | 2.0 | 3.2 |
| D | 72 | 380 | 10 | 7 | Marked in 100% | 5.3 | 2.3 | 3.4 |
| 85 | 160 | 550 | 7 | 2 | Sl. osteoporosis | 5.6 | 5.4 | 5.5 |
| E | 120 | 380 | 16 | 14 | Sl. rickets in 20% | 7.4 | 3.1 | 6.1 |
| 85-C | 596 | 20 | 16 | 6 | Atypical rickets | 7.6 | 6.0 | 6.6 |
| F | 596 | 18 | 12 | 9 | Sl. atypical rickets | 9.8 | 6.5 | 8.5 |
| G | 520 | 380 | 3 | 3 | Normal 100% | 9.8 | 9.4 | 9.6 |

Table II shows the average figures for the inorganic phosphate in the blood of rats on rickets-producing, normal and high phosphorus diets. We find that in general the reduction of the inorganic phosphate in the blood runs parallel to the degree of severity of the rachitic lesions. It will be seen also that the blood phosphate of rats (on these rather specialized diets) may be greatly influenced by the level of phosphate intake. On normal diets the range is from 5.1 to 8.2, average 6.2, and on high phosphate intake a very wide range from 6.2 to 9.8.

The dividing line between rickets-producing and non-rickets-producing diets is, however, sharp. Rats on diets containing 86 mgm. per cent. phosphorus all develop rickets and the range of blood phosphate from 2.0 to 5.0 averages usually around 3.2 mgm. per 100 cc. of blood. When as little as 75 mgm. per cent. P is added the rachitic lesions fail to appear and the blood phosphate runs an average around 5.5 to 6 mgm.

The study of the inorganic phosphate of rats under light or cod liver oil therapy brings up several interesting points. As shown in Table III, one group of rats on Diet 84 (containing 86 mgm. per cent. P) was treated with light from a mercury vapor lamp, as a preventive measure. In almost every case, complete prevention was secured but the blood phosphate, while distinctly above that of the controls, was nevertheless in the upper range of rachitic blood.

TABLE III

Prevention and Cure of Rickets
Inorganic Phosphate as mgms. per 100 c.c. Blood

| Diet | No. of Deter- minations | Treatment | Rickets | Blood Phosphate | | |
|------|----------------------------------|--------------------------------|---------------------------|-----------------|------|-------|
| | | | | Max. | Min. | Aver. |
| 84 | 18 | Untreated | Beading + to +++ | 4.9 | 2.0 | 3.2 |
| 84 | 10 | Mercury vapor lamp | Beading - to + | 5.4 | 2.9 | 4.1 |
| 84 | 8 | Codliver-oil prepara- tions | Calcification + to +++ | 5.9 | 2.4 | 3.95 |

This would seem to indicate that the rats can produce non-rachitic bone at a lower level of phosphorus intake under the influence of light than is possible without its presence.

Curative experiments with cod liver oil preparations show active calcification of cartilage going on while the blood phosphorus is still in the rachitic range. So we conclude that a definite deposition of calcium salts may occur before the blood phosphorus regains its normal level. We have as yet no experiments in which the rats were carried through till the healing process was complete, but if we can draw analogies from the work of Howland and Kramer on human rickets, we ought to find that when healing is complete the blood phosphate will regain and maintain its normal level. It seems, therefore, that calcification is not directly controlled by the level of the blood P. Experiments are now in progress to determine the nature of the relation between these two factors.

LIGHT FACTOR IN HUMAN AND EXPERIMENTAL RICKETS

ALFRED F. HESS, M.D.

As is well known, since rickets was first described there have been two different theories as to the etiology of the disease—the dietetic and the hygienic. It has been attributed to various faulty diets. On the other hand, some have thought it due to a lack of fresh air, others to a lack of exercise, still others to a lack of

light. This is the way the subject has alternated for perhaps over 250 years. One of the facts that has stood out prominently in regard to the etiology of rickets has been its marked seasonal occurrence. The condition in this regard is peculiar. In a series of four or five hundred autopsies Schmorl definitely showed that rickets occurred most markedly in the winter time, and that its curve of incidence gradually decreased, becoming lower in the late spring and still lower in the summer time. This has been the experience practically of all clinicians. This seemed a fact that might shed light on its etiology, so that a few years ago I attempted by means of the mercury quartz vapor lamp to prevent rickets by using ultraviolet light. These results were unsuccessful. On the other hand, if the diet were at fault, it might be that there was a seasonal change in the milk, which forms the main diet of children, and that the fodder of the cows might be the variable factor. An attempt to solve this aspect of the problem showed that it made no difference, as regards the incidence of rickets, whether infants were fed on dried milk which came from pasture-fed cows, or whether they were fed throughout the winter with the commercial dried milk. This study had the vitamin theory in view. There is just as much rickets among the children fed the special "pasture" dried milk as those fed the ordinary dried milk.

As you know, rickets occurs to a certain degree in over 50 per cent. of all infants, and if you include *x*-ray diagnosis the incidence is still greater. Two or three years ago Huldschinsky¹¹ in Berlin showed that by means of the ultraviolet light rickets could be cured. Last spring I tried the effect of sunlight. Cases that had developed rickets during the winter were given sunlight treatment in the early spring. They were placed from fifteen minutes to half an hour in the sunlight, being given increasing doses of this radiation. It was found in all cases that the rickets was definitely cured within a period of a month or two. This was evident clinically and by means of the *x*-ray. Following this favorable experience the same method was tried with rats. Rats were fed on the typical rachitic diet described by Sherman

and Pappenheimer. Although Diet 84 produces rickets in 100 per cent. of cases, it did not lead to rickets in rats given daily exposure to the sun of fifteen minutes to one-half hour.¹² This has been the experience of others.¹³ It was found that such exposure is about equivalent to doubling the amount of phosphorus in the food. In other words, the rickets-producing Diet 84 became practically equivalent to the rickets-protective Diet 85. You will remember that Diet 85 is Diet 84 with the addition of 75 mg. per cent. of phosphorus. If the sunlight is allowed to traverse glass, that is, if one constructs a glass box for the rats, and the light first passes through this window glass, practically no protection is afforded. Again, if the sunlight is reflected, only a slight amount of protection is afforded. This naturally led to the supposition that the ultraviolet rays play a large part in the effect. Accordingly we made use of the ultraviolet rays for rats. Radiation with the mercury vapor quartz lamp afforded complete protection. It takes about two minutes' exposure daily, at a distance of three feet, to accomplish this.

Another source of radiation used was the carbon arc lamp, the spectrum of which is very similar to that of the sun. This source of a light at a distance of three feet, when applied for three minutes, also afforded protection. In cases of scurvy light was of little or no value. We put guinea pigs on typical scorbutic diet and gave them the same amount of treatment with sunlight, but they developed scurvy just as readily as those kept in the dark.

It is impossible to state an explanation of this phenomenon. This work would suggest that light is just as valuable for the animal world as it is for the vegetable world, and we have not been considering it sufficiently in connection with disease. From the clinical standpoint it shows that if we are to get the effect of light it must act directly on the body, and that in solaria, where the light passes through glass, no benefit results in regard to the protection or cure of rickets.

CONCLUSIONS

Rats on diets high in calcium but low in phosphate develop bone lesions which are identical with those of human rickets. Rats on diets low in calcium and high in phosphate develop an atypical form of rickets in which there is a great increase in the amount of osteoid tissue in the subchondral zones, with only a slight increase in the number of cells of the zone of preparatory calcification.

On diets deficient in both phosphate and calcium, but in which the phosphate is present in relatively greater amount than the calcium, lesions similar to the atypical rickets described above are produced in most cases. Rarely lesions resembling osteoporosis are seen.

An attempt has been made to study the steps by which healing takes place under the influences of cod liver oil.

The effect of varying certain inorganic constituents of the low phosphate-high calcium diet was tried. It was found that the phosphate and not the potassium ion was responsible for the protection conferred by basic potassium phosphate.

On the type of diet used, rickets could be prevented by the addition of between 50 and 75 mgm. of P in the form of basic potassium phosphate to the rickets-producing diet,—all other factors remaining the same. The addition of various other inorganic salts did not prevent the development of rickets.

Adult rats also showed an increase of osteoid tissue when maintained on a diet low in phosphorus, but there were no endochondral changes.

The inorganic constituents were also modified. Casein did not wholly prevent the development of rickets, though the phosphorus added in this way was in excess of the amount needed for protection when given in the form of basic potassium phosphate. Lecithin protected when the 75 mgm. per cent. of P were added in this way. Yeast extract did not prevent rickets when the level of phosphorus was below the protective level—although water-soluble vitamine for growth could be given by much smaller amounts of extract.

Egg albumin did not protect. Butter and butter-fat carrying fat-soluble vitamin in amounts sufficient to prevent xerophthalmia and to promote growth did not prevent the rickets.

A diet has been used on which growth is maintained at an approximately normal rate during the experiment, and on which rickets is invariably produced.

The inorganic phosphate of the blood of rats rachitic and non-rachitic has been studied. The rachitic rats showed phosphates ranging between 2.0 and 5.0 mgm. per 100 c.c. of blood, while the rats receiving sufficient addition of P_2O_5 in the diet to protect them against rickets had phosphates of 5.5 to 6 mgm. per 100 c.c.

The blood phosphate in rats in which the development of rickets on a low phosphorus diet had been prevented by exposure to sunlight, or cured by cod liver oil, showed blood phosphates within the rachitic zone, although active calcification was occurring in the bones.

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Discussion:

DR. NORRIS: I would like to ask if the rats were white rats that were used in the experiments, and also if any sections were made of the skin after exposure, for the reason that it has been known for some time that sunlight

has an effect on the epidermal cells of the skin. Work has been done which shows that sunlight has an effect on certain diseases. Although I do not remember the special tumor, I am under the impression that one of Neusser's assistants in Vienna, Chovstek, has written an article which shows the curious relations that developed as a result of the exposure to light.

DR. WOOD: I would like to ask whether experiments have been tried to determine whether these rats show in the blood an altered distribution of phosphorus. It might be interesting to make a total analysis of the rats, both normal and rachitic, and of the rats under exposure to light, to see whether they simply redistribute their phosphorus. They may take it from one organ and put it into the blood or bone, and in that way merely redistribute the phosphorus, or they may, in the light-cured animals, make a more efficacious use of what phosphorus is given to them, and I believe that a total analysis of the phosphorus in the whole rat might give some clue as to whether the animal has stored the same, or whether he has redistributed the phosphorus in a different way.

DR. SCHWARZ: I should like to speak about twins who regularly become rachitic, and I should like to ask Dr. Hess if he has been able to protect them by sunlight. Another point is the seasonal occurrence of rickets. I think its high incidence in winter time has a great deal to do with it, and that children having nasopharyngeal infections and broncho-pneumonia very often become rachitic. Whether that starts the disease by upsetting the phosphorus or calcium or whatever the proportion was, I do not know, but that is a well known clinical fact.

DR. HESS: In this work white rats were used almost entirely. We have done some work with black rats; Professor Donaldson sent some from Philadelphia. The dosage was not made sufficiently delicate to tell whether there was any difference between the two. There may be some difference, but with the dosage of light we used both the white and black rats were protected.

As regards the pigment, there seems to me a very great difference of opinion as to its function. Some think that it has merely a protective function. Others think that it changes the short waves to long waves. Still others think it acts merely as a catalyzer. It was true that in some of these white rats the hair was a little darker. It took on a slightly yellowish color in the course of the sun treatment.

In answer to Dr. Wood, we have not analyzed the bodies of the rats for the total phosphorus. Of course most of the phosphorus is in the bone. The differences would be very small. The bones have more calcium phosphate, and that is where the calcium phosphate would be in the greatest measure. There might be a small difference.

As regards twins, there was one case where we used the sun treatment with twins and found it efficacious. I had one case some time ago, before this work came out, where I tried to cure twins, who, as Dr. Schwarz says, are especially liable to rickets, by adding a considerable amount of calcium lactate to the diet of one, and the child which got the large amount of calcium lactate was the one which developed the greatest amount of rickets. This is

explainable now, because we know that the phosphate is so much more important than the lactate.

In regard to how much the rôle of infection plays, Korenschevsky fed rats with bacteria, and was unable to produce any effect. This work on rickets was done with the idea of infecting rats, but the diet in this case was not controlled.

DR. PAPPENHEIMER: May I say one word about the question of infection? We have had seven or eight hundred rats under observation, and there has been ample opportunity for contact infection. We have never seen one case of rickets develop which could be regarded as probably due to infection. That is, in all cases the appearance or absence of rickets was directly traceable to the diet. The only way that infection might enter into the question would be that certain diets predispose to infection, as the lack of fat-soluble vitamins predisposes to keratomalacia. That is a theoretical possibility, but since we found rickets to occur on diets in which the only deficiency was phosphorus alone, we should have to assume that phosphorus-deficiency alone would predispose to infection. If so, it predisposes only to this particular infection. Though the proof is not final nor absolute, everything points against the infective origin of these lesions.

I might add in regard to what Dr. Wood said that experiments such as he suggested have been planned, and we hope to get some light on the question of distribution of phosphorus.

DR. SCHWARZ: I do not think from what we know of the clinical picture in rickets that it is only a disease of the bones. It is a disease of the entire body. I think Aschenheim showed that the calcium content is diminished in the muscle and in the brain. I am a little bit at sea as to whether you really have in these rats rickets which is comparable to that in a child. There is no question of the way in which cod liver oil helps. I should like to see some work on the various organs of these rats to get the chemical composition of the entire rat.

I think Dr. Hess and Dr. Pappenheimer must have misunderstood what I said about infection. I do not think infection will cause rickets. I know, however, that anything will cause rickets in a child which makes the child ill. When a child is not in good general shape for some reason or other it will develop rickets, and I think if you look carefully the percentage of rickets in New York City would be about 80 or 90 per cent. You will find some clinical sign of rickets in nearly all children. Almost anything will turn the balance of calcium and phosphorus. What does it, we do not know, but infection certainly does it with a great deal of regularity.

ANALYSIS OF THE FINDINGS OF EIGHT ADDITIONAL EXAMPLES OF BUNDLE BRANCH LESIONS IN THE HEART

LOUIS FAUGERES BISHOP, M.D.

(Consultant Cardiologist to the Lincoln Hospital, New York)

Since presenting to the New York Pathological Society twenty examples of bundle branch electrocardiograms which were published in the PROCEEDINGS, I have collected eight additional examples from about five hundred consecutive patients.

FIG. 1

This shows a frequency of 1.6 per cent. which is about the same as in the previous group. One of the eight cases is particularly interesting in that the records taken two and one half years previously showed the electrocardiogram to be normal.



FIG. 3

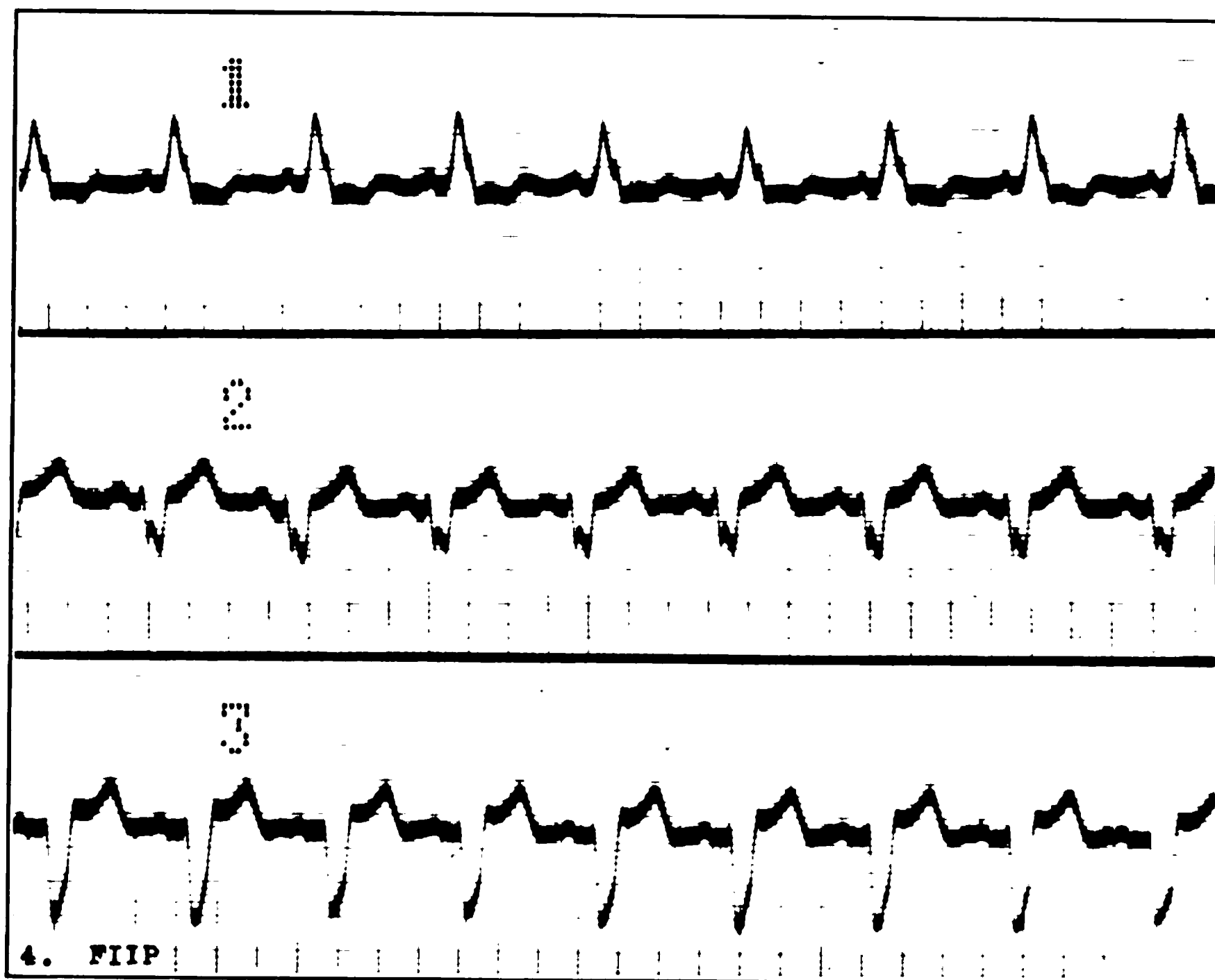


FIG. 4

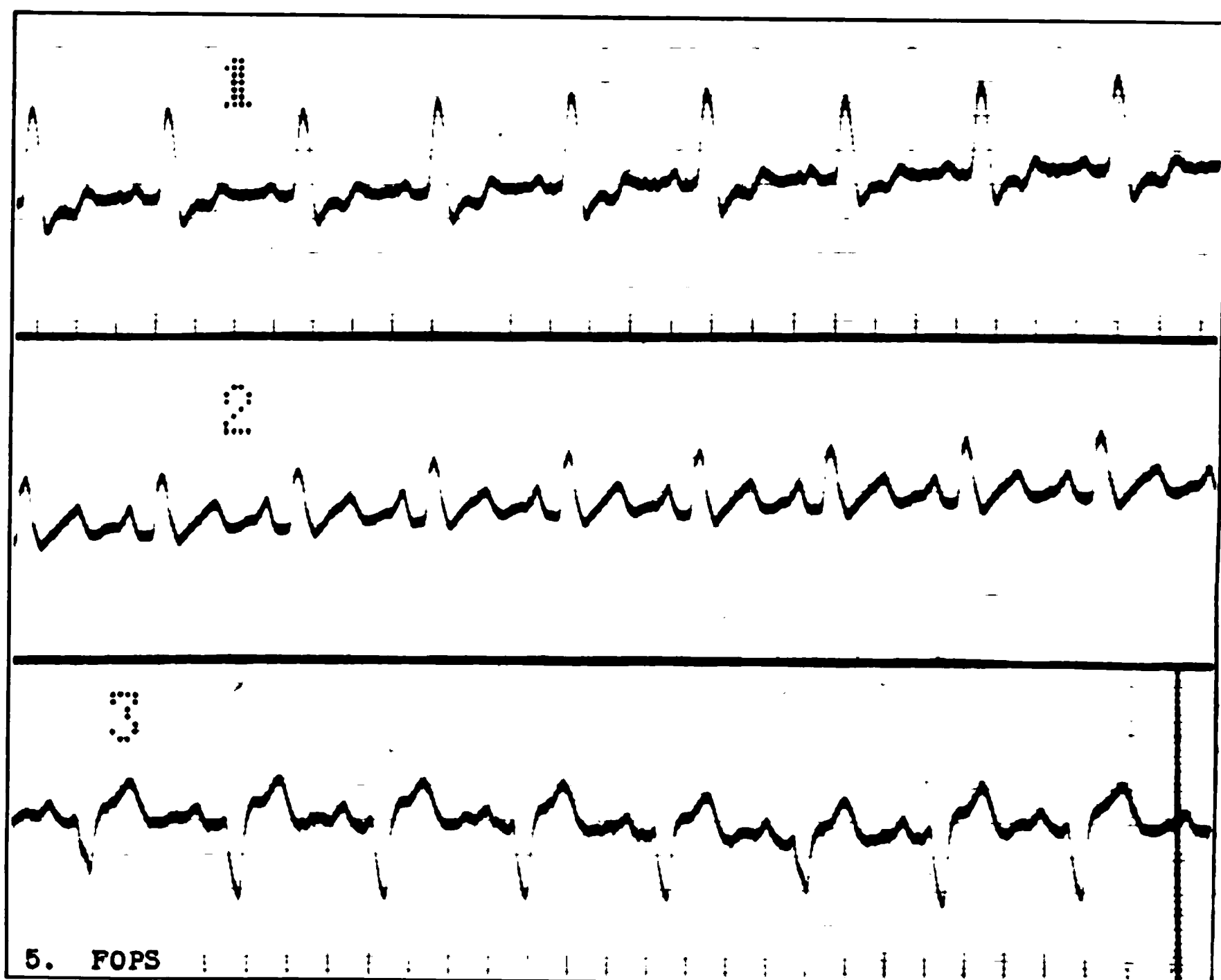


FIG. 5

FIG. 8

The clinical picture is about the same in both the groups. Some of the patients had very definite histories of a severe attack of pain, lasting several hours, followed by gradual recovery, while in others the onset did not appear so clearly in the history.

The records of these eight people fall into two groups. In group one the records are like the electrocardiogram of Case *FHHD* and show the typical characteristics that are necessary to diagnose a disease of one bundle branch which completely destroys the function. The R waves or S waves are large and wide and show notches, and the T waves are large and downward in Lead I.

The four remaining records are as in Case *FOPS* and are not so typical of this condition, but they all show marked abnormality in the notching or in the width of the R waves so that the lesion must be considered a serious one, if not complete.

Synopsis of Findings of Eight Additional Examples of Bundle Branch Lesions

| Case | Age | Sex | Probable Duration of Disease | Onset | Pain | Dyspnea | Pal-pita-tion | Cough | Ede-ma | Rhythm | Blood Pressure | Valves | Murmurs | Response to Digitalis | Size of Heart | Diagnosis | Electro-cardio-gram |
|------|-----|--------|------------------------------|------------------------------|-------------------|----------------------|---------------|-------------|-------------|-------------------------|--------------------|--------------------------|----------|-------------------------------|---------------------|---------------------------------|---------------------|
| FHHD | 76 | Male | 10 months | Pain on exertion | Yes | Yes | Yes | No | No | Irregular | 90-180 | Moderately athero-matous | Systolic | Good | Moderately enlarged | Arteriosclerosis | Typical |
| SHB | 48 | Male | 4 years | Pain referred to epigastrium | Vise-like feeling | Moderate on exertion | Yes | At times | Very slight | Normal | 160-220 | Athero-matous | Systolic | Fair | Enlarged | Arteriosclerosis | Typical |
| FBB1 | 64 | Male | 3 years | Pain and discomfort | Yes | On exertion | Yes | No | No | Irregular | 120-140 110-160 | Mitral disease | Systolic | Using strophanthus habitually | Enlarged | Advanced Cardiorenal disease | Typical |
| FIIP | 58 | Male | 2 years | Dyspnea on exertion | Yes | On exertion | None | Very slight | Yes | Irregular | 170-200 | Normal | None | Good | Large | Arteriosclerosis | Typical |
| FOPS | 61 | Female | 3 months | Pain on exertion | Yes | On exertion | Yes | No | No | Attacks of fibrillation | Systolic 80-190 | Competent | None | Good | Slightly enlarged | Cardiosclerosis hyperthyroidism | Not typical |
| FIOS | 59 | Male | 6 months | Pain and discomfort | Yes | On exertion | None | None | No | Regular | 100-140 | Competent | Systolic | Not given | Not enlarged | Arteriosclerosis | Not typical |
| FDOO | 81 | Male | 8 days | Sudden dyspnea and pain | Yes | On exertion | None | None | Yes | Irregular | 100-150 | Mitral incompetence | Systolic | Good | Slightly enlarged | Senile arteriosclerosis | Not typical |
| FSML | 63 | Male | 1 year | Palpitation | Nervous feeling | On exertion | Yes | No | No | Regular | 100-150 | Normal | Systolic | Not observed | Enlarged | Arteriosclerosis | Not typical |

The four patients with typical records complained of severe pain over the heart and all showed a greatly increased blood pressure. In the other four there was no increase in blood pressure of any extent, and there was pain in only one person of this group.

The orthodiagrams of the hearts of the individuals with typical records revealed markedly enlarged hearts of the aortic type. Only two of the patients with less typical histories showed this enlargement, the other two having enlarged hearts of the vertical type.

There was only one patient under fifty years of age in this series, he being forty-eight. All the cases were males excepting one. There was no uniformity in the duration of the disease, one man having a normal tracing two and one half years prior to the appearance of a typical bundle branch lesion. Dyspnea and precordial pain were present in all eight people, the precordial pain being most marked in those who had definite bundle branch tracings. These attacks, which were intermittent, came on usually by exertion. In one person it was the chief complaint which brought him for examination. Only two of the typical bundle branch cases were bothered with cough which no doubt was brought on by some congestion in the lungs. The heart valves were not primarily involved in one half of the patients.

Discussion:

DR. PAPPENHEIMER: I would like to ask if these cases were the result of coronary sclerosis or rheumatic myocarditis.

DR. BISHOP: They were almost all the result of coronary sclerosis.

A. D. Hirshfelder gives a very good description of coronary sclerosis in his book on "Diseases of the Heart and Aorta," as follows:

"While the sclerosis of the coronary arteries does not differ in its pathology from the sclerosis of arteries elsewhere, nevertheless the action upon the heart gives rise to clinical and to secondary pathological conditions which are quite different from those of general arteriosclerosis, and which therefore deserve special consideration.

"Another important condition which is very common is arteriosclerotic or atheromatous change arising in the aorta with or without associated involvement of the coronaries themselves, but spreading so as to involve the mouths of the coronaries as they arise from the aorta, and strangulating these vessels as they pass through the aortic wall. This has the same effect as a

metal band constricting an artery would have; namely, of diminishing the blood pressure and the velocity of flow in the artery beyond it, of allowing the walls of the artery to contract down and hence of producing a further permanent secondary narrowing of the lumen, with progressive diminution of the blood supply to the part (Halsted). The course of the artery may show patches of hardening with indentations and widenings, collar-like constrictions or uniform widenings; or on the other hand, the arteries may be converted into uniform tubes whose walls may give the sensation of rubber tubes on the one hand (uniform fibrous sclerosis), or of absolute pipe-stems (complete calcification) on the other. This condition is, of course, particularly common in arteriosclerosis affecting the base of the aorta, *i.e.*, luetic aortitis and luetic aortic insufficiency, and may account for many other symptoms.

"Since the heart muscle requires much more blood when it is beating forcibly and rapidly than when it is beating slowly and quietly, it is easily seen that this collateral circulation may be sometimes adequate and sometimes not. Also, since in different individuals of the same species there are variations both in the structure and disposition of the minute arteries and in the needs of the muscle fibers for nourishment, it is but natural that the results of coronary disease should vary greatly."

109 EAST 61ST STREET

CONGENITAL STENOSIS OF THE DUODENUM ASSOCIATED WITH DEXTROVERSION OF THE AORTA

LUIGI CELANO, M.D.

The uncommon association of cardiac and intestinal congenital malformations seems to me sufficient apology for the report of this case.

The patient was born of a healthy woman of 33, who had had one child seven years before and no miscarriages and who had been operated for retroflexion of the uterus three years before. The pregnancy was uneventful, except for a slight degree of cyanosis.

Parturition was precipitate. The child, a puny female of five and one half pounds, was reported as normal by the interne, but probably was not examined, at the time of delivery. She nursed well in the first three days. On the night of the third day, the infant developed a temperature of 105° F. ascribed by the internes to starvation. The child was given castor oil and had a dark bowel movement in the morning and the temperature dropped to 100. On the fourth day, the temperature went down in the morning and up again in the afternoon and the child vomited. A careful examination was then made. The child looked ill. She was not cyanotic, breathed not too rapidly, 30 to 35 respirations a minute; the abdomen was markedly distended, bulging mostly

in the epigastrium. No visible contractions were noted. The cord was sloughing and pus was oozing from the umbilicus around the stump. On auscultation there was a loud systolic murmur heard over the whole precordium. The murmur was harsh and prolonged. The lungs were clear. Antiseptic treatment was given the cord which the next day looked much better, but some nodules were thought to be felt along the umbilical vessels going up to the liver. On that day (the sixth) the child vomited a few times but not forcibly.

The bowels moved again after enema and some yellow material was expelled suggesting that milk had been digested and passed down the gut. There was never the slightest suggestion of jaundice or cyanosis. Obstruction and congenital heart disease were thought of, but all things put together pointed more to infection of the cord with complicating peritonitis, septicemia and endocarditis.

On the seventh day the child died.

At autopsy the stump of the cord appeared necrotic and oozing pus, but without inflammation around it. On opening the abdomen the peritoneum was

FIG. 1

perfectly normal and so were the umbilical vessels, and the liver. The diaphragm was at the fifth rib on the right side, at the fourth interspace on the

left. The thoracic organs were all normal except the heart. This organ weighed 26 grams. The outside appearance was normal. On opening the right side the right auricle presented a fenestrated membrane at the place of the foramen ovale. There were several punctate perforations and an opening about 3 mm. in diameter, at the lower end. The tricuspid valve appeared normal, and the auricular ventricular ring was 5.5 cm. in circumference, but behind the left cusp the lumen of the ventricle was continued into the aorta. The walls of the conus arteriosus were thick and its lumen very small. The pulmonary orifice was 1 cm. in circumference and the valves white in color and somewhat thickened. The aortic orifice was 24 mm. in circumference and the aortic valves normal. On opening the left heart the auriculo-ventricular ring was 3 cm. in circumference and the mitral valves normal. Behind the anterior valve the lumen of the ventricle was continued into the aorta. The membranous part of the interventricular septum was absent. In the lumen of the pulmonary artery, right back of the bifurcation, there was a minute dimple. No other trace of the ductus arteriosus could be found. The stomach and about the first two and one half inches of the duodenum were enormously distended. The pylorus was perfectly evident but also distended. Right at the entrance of the common bile duct there appeared to be a constriction and all the rest of the intestine below it, small and large, was completely collapsed. On exerting pressure on the stomach or on the distended part of the duodenum, some of the contents could be squeezed into the intestine below the constriction. The head of the pancreas rested around the posterior part of the constriction. On opening the stomach the contents seemed to be practically all milk and there was no bile mixed with it. The intestinal contents below the constriction resembled ordinary meconium.

Close to the entrance of the common bile duct a diaphragm-like occlusion was present.

The circumference of the duodenum above the occlusion was 6 cm. The circumference of the pylorus was 3.5 cm. The circumference of the duodenum below occlusion was 2.5 cm. The surface of the diaphragm-like occlusion toward the stomach a little to the left of the center showed a round depression 8 mm. in diameter, devoid of mucosa, and leading obliquely downwards and to the right in a sinus-like channel which appeared on the distal surface in a slit-like opening, about 1 cm. in length. A small probe could be easily passed through the opening. The pancreas was closely adherent to the posterior surface and each side of the duodenum, at the same level of the occlusion. On the anterior surface at the same level there seemed to be a thickening of the wall. The condition looked similar to an invagination of the mucous membrane by means of a constricting ring-like band. The walls of the duodenum and stomach were extremely thinned out and the folds of the mucosa stretched and flattened. The common bile duct seemed to run with its lower end right through the pancreas and empty within the sinus, in the occlusion.

The heart resembled the typical condition of pulmonary steno-

sis with dextroversion of the aorta and incomplete interventricular septum.

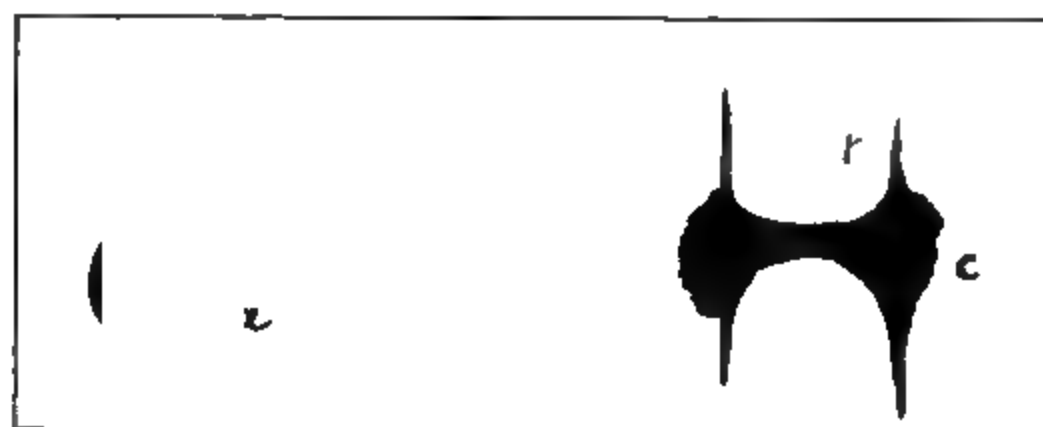


FIG. 2. Diagram of stenosis. *a*, Distal view; *b*, proximal view; *c*, longitudinal section; *r*, connecting tract.

Two explanations can be offered in such cases: (1) Developmental. (2) Inflammatory.

In the developmental explanation it is assumed that the aortic septum for unknown reasons fails to come down and meet the interventricular septum and also divides unequally the truncus arteriosus, thereby leaving a stenosed pulmonary orifice and a communication of both ventricles with the aorta.

In the other explanation an inflammation is assumed causing stenosis of the pulmonary artery before the eighth week of development, that is, before the formation of the interventricular septum. In that way the blood in the right ventricle, finding difficult exit through the pulmonary artery, causes increased pressure in the right ventricle, thereby pushing the septum to the left and bringing the lumen of the right ventricle under the aorta where it finds a freer outlet.

The appearance of the endocardium and the pulmonary valves rather favors the second explanation.

The etiology of the congenital obstruction is still more obscure.

It occurs among newborn children once in 20,000 to once in 50,000 times.

Davis and Poynter in a collection of 431 cases showed the following distributions:

| | |
|-----------------------|-----|
| Duodenum | 134 |
| Jejunum | 60 |
| Ileum and Cecum | 101 |
| Colon | 39 |
| Multiple | 67 |

In reviewing the literature, almost every author gives a different explanation, but here too two main factors must be considered: (1) Disturbed development. (2) Inflammation.

In the first factor the main point to be considered is the failure of recanalization of the intestinal tube after the period of hyperplasia of the mucous membrane. Another point in connection with development is the possibility of accidents during the growth of the canal. Fetal inflammations when demonstrable give the easiest explanation.

In my case the condition would point more to a kind of developmental accident.

Microscopical sections taken through the long axis of the duodenum and through the occlusion show the occlusion like a shelf protruding within the lumen of the gut. The mucous membrane from each side of the duodenum

is continuous on the corresponding side over the shelf. The shelf itself between the two layers of mucous membrane consists of connective tissue containing tubule-like structures resembling pancreatic or bile ducts, and many relatively large blood vessels. A few broken up muscle fibres were also present. The pancreatic tissue is close to the side but not within the tissues of the occlusion. The mucous membrane on the upper surface contains glandular elements similar to those of the duodenum. That of the lower surface is more papillary in form and more similar to the mucous membrane of the jejunum.

Considering the position and structure of the occlusion with the presence of duct elements in it, one is justified in suspecting that the formation of the pancreas may have had something to do with the production of the constriction.

The pancreas develops from at least two outgrowths from the duodenum, a dorsal and a ventral, the last one being connected with the bud of the common bile duct. Some authors sustain that there are up to four outgrowths. It is not hard to figure out that during the process of fusion of those embryonic parts of the pancreas coming out from different points on the circumference of the gut, the organ may undergo torsion on its long axis, or its walls may be held in at some point, while the distal and proximal parts of the organ grow and enlarge freely, and a condition similar to the one found in my case may be produced.

Discussion:

DR. FRASER: I have seen the sections of Dr. Celano's case and I think that the histological picture suggests that the constriction may have been brought about by pulling and twisting of the gut wall by means of the outgrowth and later convergence of the two pancreatic ducts. The lesion, as was seen in the lantern slide, is really an invagination of the wall as if by a constricting band, on each side of which is a pancreatic duct. Now it is not difficult to imagine how these ducts originating at different points in the circumference could in the process of their outward growth and effort to get together produce such an invagination of the portion of the wall lying between them in some such way as that suggested by Dr. Celano in his first explanation. The other suggestion, that the constriction is due to failure of complete canalization of the mucosa of the once more or less solid duodenal tube, does not seem to fit the picture here presented. In such a case we should expect an abnormally thickened mucosa by epithelial hyperplasia or fibrosis, whereas the different layers of the wall are normal and all invaginated together.

DR. MACNEAL: I think constrictions of this sort, though perhaps less rare at the particular site mentioned, also occur in other parts of the gut, and the

explanation of these other obstructions is, it seems to me, extremely difficult on the basis of a pancreatic diverticulum. We recently saw an obstruction in an infant three weeks old who never had done well and who came to the Hospital for intestinal obstruction. The surgeon operated on the case and made a diagnosis of tumor at the lower end of the ileum, and all he did was to connect the ileum to the ascending colon. The child died, and the specimen showed an enormous thickening of the wall at the lower end of the ileum for three cm., and there seemed to be a small cyst or diverticulum into the wall. The mucous membrane was almost completely disintegrated. It might have been something similar to this case. We were unable to decide what caused the condition. The surgeon thought it was a tumor growth but the microscopic examination showed only inflammatory changes, coupled with hypertrophy of the muscular coat. There was evidently obstruction which had proceeded from some maldevelopment. I am inclined to think that these may occur as anomalies in other parts of the intestine. Possibly the region of the papilla of Vater and the ileo-cecal junction may be particularly predisposed to such congenital stenosis.

TETRACHROME BLOOD STAIN: AN ECONOMICAL AND SATISFACTORY IMITATION OF LEISHMAN'S STAIN

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Since Leishman,¹ in 1901, modified Jenner's blood stain by substituting for methylene blue a methylene blue which had been partly decomposed by treatment with dilute alkali and heat (Nocht's polychrome methylene blue), there have been numerous imitations and slight modifications of this stain described by various workers. In this country the best known of these is the modification of Wright.² The results obtained in actual staining by the use of these various modifications are, as a rule, inferior to the pictures obtained by the original stain of Leishman.

In 1905 and 1906³ it was shown that the essential dyes of the Romanowsky stain, of which the Leishman stain is a special application, are four in number, rather than three as had been previously maintained by Giemsa.⁴ These four dyes are eosin, methylene blue, methylene azure and methylene violet. The two

last mentioned substances were first prepared and named by Bernthsen⁵ in 1885. Either methylene azure or methylene violet, in combination with methylene blue and eosin, will produce the red nuclear tint characteristic of the Romanowsky stain. However, the most brilliant and satisfactory results in the staining of blood are obtained when all four dyes are utilized.

Water-soluble yellowish eosin and medicinally pure methylene blue are easily obtainable and are not expensive. Methylene azure, which is now made in the United States by oxidizing methylene blue with chromic acid and heat, is also easily obtainable at a price of 40 to 50 cents a gram, although the German product, Giemsa's Azur I, used to cost five times that amount. A satisfactory preparation of Bernthsen's methylene violet is more difficult to get and it is not listed by the ordinary dealers in dyes. The preparation of an impure methylene violet is not difficult, but its purification by recrystallization from alcohol is difficult and time-consuming. Fortunately the impure, crude substance gives good practical results in staining of blood films.

Crude methylene violet is prepared by dissolving 20 grams of medicinally pure methylene blue in nine liters of water and then adding 20 grams of crystalline sodium carbonate, previously dissolved in one liter of water. The mixture is then heated to boiling for five to ten hours. The precipitate of long needle crystals is filtered out, washed with distilled water, and dried on a porous plate. The yield is about 5 grams (25 per cent.). This substance is crude methylene violet. The chief impurities are methylene blue and methylene azure and lesser amounts of difficultly soluble, unidentified substances. These impurities do not seriously impair the usefulness of the product.

In collaboration with Schule,⁶ in 1913, it was determined that a mixture of the following composition gave most excellent results in the staining of blood cells and hematozoa.

| | |
|--|-------------|
| Water-soluble eosin | 1.0 gram |
| Medicinally pure methylene blue | 1.0 |
| Methylene azure, recrystallized | 0.6 |
| Methylene violet, recrystallized | 0.2 |
| Pure methyl alcohol (Merck's Reagent)..... | 1000.0 c.c. |

At that time we recommended the preparation of the stain in two solutions, keeping the eosin separate from the other three dyes, and mixing the two solutions in equal parts shortly before use. The separate solutions keep well for two years, but not for four years. The deterioration appears to be due to the slow oxidation of the alcohol. This change is more rapid when the four dyes are present in the same solution. For the last nine years these solutions have been employed in the routine staining of blood films at the Post-Graduate Laboratories, crude products of methylene violet being substituted for the highly purified sample employed in the original tests.

Since 1919 an attempt has been made to interest American dye chemists in the manufacture of methylene violet and particularly in the preparation of a finely ground mixture of the four dyes in a dry state, ready to be dissolved in methyl alcohol in the proportion of 3 grams to a liter of alcohol. For this mixture of the four dyes the name Tetrachrome Blood Stain has been suggested. Crude methylene violet is used in double the quantity indicated for the pure substance in the above formula.

One manufacturer¹ has prepared a satisfactory mixture of this sort which is designated as tetrachrome blood stain and priced temporarily at one dollar for ten grams, enough for more than three liters of staining solution. An effort is now being made to interest other manufacturers and dealers.

This stain is recommended as a satisfactory imitation of the Leishman stain because of the excellent results in staining blood films, the uniformity of composition and the low cost. The latter is of some importance in large hospitals where many specimens have to be examined daily.

References

1. LEISHMAN: *Brit. Med. Jour.*, 1901, ii, 757.
2. WRIGHT: *Jour. Med. Research*, 1902, vii, 138.
3. MACNEAL: *Jour. Inf. Dis.*, 1906, iii, 412.
4. GIEMSA: *Centralbl. f. Bakt.*, 1902, xxxi, 429.

¹ Calco Chemical Company, 136 Liberty Street, New York.

The National Aniline and Chemical Company, 21 Burling Slip, New York, has recently prepared this stain also.

5. BERNTHSEN: *Liebig's Annal d. Chemie*, 1885, ccxxx, 137.
6. MACNEAL AND SCHULE: *The Post-Graduate*, 1913, xxviii, 982.

Discussion:

DR. EWING: I think Dr. MacNeal has done a distinct service in bringing this before us. Does it stain spirocheta well? Have you tried it on tissues?

DR. MACNEAL: Yes. I haven't done anything with tissues; perhaps it would work out, but I haven't tried it.

BLOOD CHANGES IN MYELOGENOUS LEUKEMIA FOLLOWING RADIUM TREATMENT

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Dom Etienne Gilbert in the Paris *Theses* of 1914 describes a number of cases of myelogenous leukemia treated by radium, in which excellent results took place, the red cells increasing to their normal level and the leucocytes decreasing to nearly their normal level with general improvement of the patient's health. But ordinarily, the cure, according to Gilbert, is not stable, the signs of leukemia often reappearing after some weeks have passed, and with radium treatment the number of leucocytes diminishes less rapidly, the curative action of radium very likely being weakened.

G. Lovell Gulland in the *British Medical Journal* of August 30, 1921, describes the treatment of myelogenous leukemia with radium, and while he cannot say the benefit has been permanent, it has been certain and more rapid than that of *x-ray*. The first obvious effect has been a reduction of the leucocyte count, the neutrophiles, both the polymorphonuclear and myelocytic forms being most affected in this decrease. Next are the eosinophiles and basophiles while the lymphocytes and mononuclears are less affected. The nucleated red cells practically disappear, and in successful cases the blood may return to a nearly normal appearance. The spleen grows smaller although it never goes back to its actual normal size, for with its increased fibrosis one would scarcely expect it to do so.

Dr. James Metcalf in the same journal regards radium as of excellent value in leukemias, especially the myelogenous form, and mentions the case of a man of fifty-nine, afflicted with the latter, who showed marked improvement from radium treatment. The radium was applied over the spleen, sternum, and epiphyses of the femora and humeri. He believes that the doses must be massive and frequent as small doses only stimulate the abnormal conditions.

Within the past two years at the Post-Graduate Hospital studies have been made of the blood changes in myelogenous leukemia following radium treatment as will be seen in the following case.

CASE I. William E. —, aged 14. He first came to the Post-Graduate on April 27, 1920, with the following clinical picture.

His family and previous history were negative.

In July, 1919, his mother noticed that he did not play with his former vigor and energy, and that he was pale and complained of weakness and loss of appetite. He was examined and given medicine by a physician and continued to decline in health. In October he was sent to the Staten Island Hospital for an enlarged spleen; he remained there for a month, but was afterwards discharged with a bad prognosis.

Physical examination showed the patient to be thin and generally anemic in appearance. The lungs and heart were negative except for a soft systolic murmur of the latter at the second interspace. The abdomen was protuberant and distended by a large mass on left side, firm in consistency, extending obliquely downwards from the left hypochondrium to within 25 cm. of the pubic symphysis. The liver was palpable 8 cm. below the costal margin. No free fluid was made out. The superficial veins were prominent over the entire body, especially over the abdomen and lower extremities.

The Wassermann test, taken April 27, was negative.

Provisional diagnosis: Splenomyelogenous leukemia.

On April 28, the first blood count was taken which showed 3,150,000 red cells per cubic mm. and 164,800 leukocytes and 50 per cent. of hemoglobin. A differential count of 500 white cells showed 35 per cent. of polymorphonuclear neutrophiles, 36 per cent. of lymphocytes, mononuclears and transitionals, 7.2 per cent. of eosinophiles, 7.6 per cent. of basophiles, 37 per cent. of neutrophilic myelocytes, 7.4 per cent. of eosinophilic myelocytes, 3.2 per cent. of basophilic myelocytes and 4 per cent. of myeloblasts. A few normoblasts and macroblasts were seen among the red cells. Some more smears were taken two days later which showed a similar blood picture, with an occasional myelocyte undergoing mitosis.

On April 29th, at 4 P.M. 100 mgm. of radium were applied over the region of the enlarged spleen, the dose being changed every hour in fourteen succes-

sive applications. On May 4th the leucocytes had fallen to 135,400, but two days later, the blood count showed a rise in the leucocyte count to 312,000, but another count taken on the following day showed a fall to 202,000.

The second dose of radium was applied on May 10th, when 100 mgm. were applied, beginning at 3:50 P.M., in twelve successive applications.

By May 13th the leucocyte count fell to 199,000; two days later it had fallen to 162,000 and by May 20th it was 77,400.

On the 26th it was found that leucocytes had increased to 118,400 and on this date 120 mgm. of radium were applied over the spleen in eleven successive doses. The leucocyte count began gradually to diminish, going down to 112,000 by June 1st and 111,000 by June 3d. On that date 120 mgm. of radium were applied in seven successive applications of two hours each. On June 7th the leucocytes had diminished to 52,000 while the red cells had increased to 3,926,000. On June 8th the patient was discharged.

On July 2d he returned for examination and treatment. The spleen was now greatly reduced in size, the splenic notch being 9 cm. from the tip of the xiphisternum, the lower border 14 cm. from the ninth costal cartilage and the right border 14 cm. from the median line. The leucocytes had fallen to 12,000. On the sixth 120 mgm. of radium were given at 10 A.M. in four successive applications of two hours each. He returned on Sept. 9th and the leucocytes were found to have increased to 28,400. He was now given 60 mgm. of radium in eight successive applications for sixteen hours. On Oct. 7th when he came again the leucocyte count was the same, but the polynuclear neutrophils had risen from 14,484 to 17,792 and the lymphocytes and mononuclears had risen from 1,420 to 8,400, while the myelocytes had fallen to practically nothing. On Oct. 28th, when he came again for treatment, he showed a decided improvement, the leucocyte count being 15,400 and the blood picture appearing much more normal. The spleen was firm and palpable and the patient had gained ten pounds in weight, his weight now being 79 pounds.

During the winter and spring the patient called at intervals of nearly every month for treatment, and on each visit he was given radium in five successive applications of three hours each. The polymorphonuclear neutrophils approached more nearly their normal level, and the myelocytes showed a marked decrease, none being found in the differential counts taken in February and March, and only a few being found in the count of May and June. The patient's general condition was greatly improved, the anemic pallor and prominence of the superficial veins being gone, and the spleen was reduced to nearly a quarter of its former size.

The patient was away in the country during the summer, but returned for treatment on September 1st. Here it was found that the leucocyte count was 69,800 per c.mm. with an increase of myelocytes above the lymphocytes, so he was given 90 mgm. of radium for eighteen hours in six applications. He returned a week later for treatment and this time the leucocyte count was 20,000. He was given 100 mgm. of radium in four successive doses of four hours each.

On September 29th the patient came to the hospital with weakness, drowsi-

ness, loss of appetite and fever, and a herpetic sore on the lower lip. The leucocytes had risen to 58,200 but the differential count showed a striking contrast in that the polynuclear neutrophiles had fallen to 4 per cent. or only 2,328 while the lymphocytes had risen to 35,596 or 68 per cent. The patient bled occasionally from nose and rectum. The red blood cells were 2,328,000. On October 7th the leucocytes had fallen to 1,800 and the anemia was more marked. The sore on the lower lip had formed an ulcer the size of a silver dollar, and this was diagnosed as gangrenous septic dermatitis following deep infection of the herpetic sore, which the patient was unable to resist on account of the leucopenia. By October 18th the leucocytes were 310, the red cells 1,148,000 and the hemoglobin 23.5 per cent. On October 25th the patient was transfused with 500 c.c. of blood, but improvement was only temporary. On November 1st the red cells were 1,252,000, the hemoglobin 24 per cent., and the leucocytes 380 per c.mm. of which there were 18 per cent. polynuclear neutrophiles, 70 per cent. lymphocytes, and 12 per cent. basophiles. The patient died that night at eleven o'clock.

The autopsy performed the next day at 9 A.M. showed the following:

Gross anatomical findings. Abdomen: Two thousand c.c. of opalescent yellow fluid containing fibrin flakes were in the abdominal cavity.

The spleen was enlarged, weighing 780 grams, adherent to parietal peritoneum beneath cutaneous scars, and contained deep fibrous scar tissue sending fibrous trabeculæ into the splenic substance.

The liver weighed 1,930 gm., the capsule was thickened and lobules enlarged.

The posterior mesenteric vein and tributaries were congested. The mesenteric and retroperitoneal lymph nodes were brown and moderately enlarged.

There was gelatinous edema of the retroperitoneal tissue behind the ascending colon with gas bubbles and putrefactive odor, evidently due to agonal invasion of anærobic bacteria.

Thorax: There was two hundred c.c. of clear yellow fluid in each pleural cavity.

Posterior portions of both lungs showed edema, with a firm airless reddish-brown nodule in the upper lobe of the right lung.

Small petechial hæmorrhages were in the parietal layer of the heart and beneath the pericardium. The heart muscle was pale.

The yellow marrow of the long bones was replaced by dark red marrow.

Microscopic Findings: Spleen: The capsule showed dense fibrous thickening with thick fibrous scar tissue extending into the splenic substance by irregular fibrous trabeculæ, infiltrated along the borders with hemosiderin granules. The Malpighian corpuscles were largely replaced by fibrous connective tissue and the splenic pulp was infiltrated by a fibrous network with many sinuses and capillaries. Only a few small patches of round cells resembling splenic pulp, and occasional accumulations of red cells were found; many round cells, few polynuclear and eosinophile cells and very few myelocytes were found. The red cells in the vessels were very scanty and there was evidence of hemolysis.

Bone marrow: Smears from the marrow of the third lumbar vertebra showed out of a count of 200 cells, 12 polynuclear neutrophiles, 112 lymphocytes and mononuclears, eosinophile, 4 basophiles, 26 neutrophilic myelocytes and 33 disintegrated cells. Occasional nucleated red cells were seen. In the section the marrow consisted of ragged masses of red corpuscles, including many normoblasts with occasional macroblasts and few megaloblasts and rarely a giantoblast. Neutrophilic and eosinophilic myelocytes and occasional polynuclear cells were seen, with large numbers of nongranular mononuclear cells greatly outnumbering the myelocytes and the polynuclears.

Smears from the shaft of the femur showed out of a count of 200 cells, 8 polynuclear neutrophiles, 114 lymphocytes, 6 eosinophiles, 3 basophiles, 12 neutrophilic myelocytes, 3 eosinophilic myelocytes, 1 basophilic myelocyte and 33 disintegrated cells. During the count 19 normoblasts, 7 microblasts, 4 macroblasts and 1 megaloblast were found. In the sections the marrow substance showed a more compact mass of cells than in the third lumbar vertebra. The myelocytes and polynuclears were more abundant and large numbers of nongranular mononuclear cells were seen. Sections from a rib and from the sternum showed a similar appearance to that of the third lumbar vertebra, except that the myelocytes and polynuclears were more scanty.

Liver: Some of the cells contained minute fat particles brought out by Scharlach R. stain. In a few places hemosiderin granules were found in the intercellular channels. In one area these channels were distended into spaces resembling alveoli, from 1/40 to 1/10 mm. in size, evidently having formerly been distended with accumulations of myelocytes.

In the mesenteric lymph nodes the lymphoid tissue was mingled with red cells, largely disintegrated. In some glands there was an increase of fibrous connective tissue in and around the lymphoid tissue with some thickening of the vessel walls.

Lungs: In a section including the nodular portion, the alveoli were solidly filled with blood, but some contained plasma with few red cells, many of these being disintegrated. The alveolar capillaries were much engorged. Very few leucocytes were found, except endothelial cells, of which there were many.

In conclusion it will be seen that while the patient was being greatly benefitted for the time by the radium treatment, its effects were temporary and when the patient discontinued treatment for two months, he suffered a relapse. His subsequent condition showed the need of using the utmost caution in giving radium treatment, especially after a relapse, because then the resistance is so apt to be lowered. While the first dose of radium after the patient's return did bring on an apparent improvement in the blood picture, the most striking phenomenon after the second dose was the rapid fall in polynuclear leucocytes, the blood picture almost resembling lymphatic leukemia, and the rapid

leucopenia and anemia which followed, resulting in the patient's death.

Discussion:

DR. MOSHCOWITZ: I have no experience in treating leukemia by radium. It seems to me that from the pathology of the disease the application of radium to the spleen alone, or even to a portion of the bone marrow, could hardly affect the malady to any great extent. Certainly Dr. Witcher has obtained some changes in the blood picture by the use of radium to the spleen, but whether the change in the blood picture is an indication of the change in the leukemic process I venture to doubt. We have all seen changes in leukemia by the use of other methods than that of radium. You will recall the striking changes after the use of benzol, but these are entirely temporary, and have no permanent effect on the patient. It seems to me that if radium is to prove beneficial in leukemia it must be applied in a form which will reach every portion of the reticulo-endothelial apparatus.

It was especially interesting to me to note the transformation of the case from a leukemia to a leukanemia. It seems to me that this transformation resulted from an exhaustion of the bone marrow and consequent interference with hematopoiesis. It shows what I have always suspected, that leukanemia was not a disease in itself, but was simply a terminal phase of a leukemia, or perhaps of a pernicious anemia in which a compensatory terminal stimulation of the bone marrow led to the presence of embryonal forms of leucocytes in the blood.

DR. EWING: I think Dr. Moschcowitz's conception of the pathology of the disease forms the only sound basis for any attempts at therapy, either by radium or by any other agent. Since we know the essential lesion is located in the bone marrow, and pretty much in all the bone marrow, we might very well ask what is the use of applying a little radium to a big spleen. However, our theories receive a jolt when we actually witness the transformation of the patient clinically who has received a little radium over an enlarged spleen; the improvement is often quite remarkable, and in some cases it has lasted very much longer than in that reported to-night. Our work at the Memorial Hospital has led us to the conclusion that Dr. Moschcowitz mentions, that unless we have a constitutional agent, we cannot hope to find a cure for the disease. Therefore in several cases we injected a solution of radium deposit into a vein. That would give all the effects of the alpha, beta, and gamma rays. In several cases of leukemia treated in this way there were sharp constitutional reactions, with very pronounced changes in the circulating leucocytes, and a rather long continued improvement in the condition of the patient. I think most of those cases are now dead. They were treated three or four years ago, but I know of one woman who is still living and apparently well. The details of her blood picture I cannot give. However, that method failed notably in a certain case which came to autopsy, for reasons which were perfectly definite. We found the bone marrow everywhere solidly packed with cells like a leukosarcoma. There were large deposits of tumor-like masses in the liver, and the lymph nodes were firm and filled with large cells. Histologi-

cally we called it a leukosarcoma, and of course the local application of radium is not going to cause a regression of a universal leukosarcomatosis. On the other hand, there was such a remarkable, although temporary, change in the clinical picture in this case that it would seem that the local applications do have some peculiar constitutional effect which is very difficult to explain. It has recently been suggested that the best method of regulating dosage is by observation of the total metabolism of the patient as indicated by the urinary nitrogen. When it comes to normal, do not attempt to add to the effect by increasing the dosage. Disregard the leucocyte count, and treat the patient rather than the leucocytosis. I am not prepared to say anything about this method, but Dr. Stone at the Memorial Hospital has come to the conclusion that it is best to treat these cases very cautiously.

DR. MACNEAL: It seems to me that the importance of presenting a case of this sort is to bring out discussion. If anyone understands clearly how radium affects the pathological process, and the exact pathology of leukemia, I should like to learn it, and therefore I feel that discussion is tremendously important. I also feel that reports concerning the results of treatment of leukemia by radium are valuable, especially when the full returns are in, as in this case, and that those cases which were last observed alive after a period of treatment of one or two years are less valuable. I have very grave doubts as to the eradication of the pathological condition by any method of treatment in the case of leukemia. My enthusiasm for publication of the report presented by Dr. Whitcher increased after the patient died, as I regard such a completed case as much more valuable. Concerning the effect which radium has on the disease by the mere local application to the spleen, I think there cannot be very much doubt about it. It really does produce changes in the blood. In regard to the treatment of the long bones by radiation, x-ray or radium, I might say that in the early days there was a good deal of enthusiasm in giving larger, strong doses to the long bones as well as to the spleen, and the results were so effective that we did not feel like bringing them before any society; the patients promptly died. One has to be extremely careful about the amount which is applied in these cases. Whether it is wiser to give minute doses over a large area of the body, or rather a severe burn over the spleen is debatable. In the case here reported the patient lived for over a year under observation. He had a vacation and went to the country. Upon his return he was actually not so well, and the attempt to make up for lost time by giving him heavy doses was followed promptly by a very unfavorable change in his condition.

DR. WHITCHER: In regard to applying radium over the long bones, we discontinued that at the Post-Graduate Hospital, because the danger is that it will have a destructive effect on the marrow of the bones, so that it prevents the marrow from producing new red blood cells and hemoglobin, and so does more harm than good. The principle of applying the radium over the spleen is to stimulate the fibrosis in that organ, and so check the growth of myelocytes there, which, where there is no fibrosis, goes on unchecked, the cellular tissue of the spleen not being held under the limitations that the marrow of the bone is, according to Dr. Cabot's theory. He claims that in the spleen

the marrow cells are not held in check as they are in the bone marrow, so the spleen grows larger and larger, unless fibrosis takes place, and where that takes place, it retards the growth of the organ and the patient's life is prolonged; so that evidently the principle of applying radium over the spleen is in the stimulation of fibrosis and its effect on the disease. I think it likely when the patient came back and had the first dose of radium, and the cells dropped to 20,000, that if he had only been given a smaller one or allowed to go without it for the time, his life might have been prolonged, but such a large dose acted as too much, just as a severe pyogenic infection overwhelms the patient, by its overstimulation and toxic effect upon the bone marrow, destroying its ability to produce new cells.

A CASE OF SPINDLE-CELL FIBROBLASTIC SARCOMA OF THE THYROID GLAND

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Sarcoma of the thyroid gland takes on a new interest since Dr. Ewing has said in his "Neoplastic Diseases" under the title "Sarcoma of the Thyroid Gland": "the occurrence of true sarcoma in man still requires demonstration." In any event primary sarcoma of the thyroid gland is of sufficient rarity to justify the presentation of what we believe to be a true spindle-cell sarcoma of the thyroid gland.

Spindle-cell sarcoma of the thyroid, classified according to the morphology of the cells, has been reported about once a year since 1876. Foerster had recorded one in 1860 and Mueller one in 1871, both giving detailed histological descriptions. Luecke in 1875 refers to reports of spindle-cell sarcomas. Doléris and Socin, in 1876, each reported a spindle-cell sarcoma and, in 1879, sarcoma of the thyroid was given important consideration by Kaufmann, who referred to the spindle-cell sarcomas of Mueller and Rose and reported one of his own. Kaufmann's classical description of spindle-cell sarcoma has been the basis of most later microscopical studies. He was one of the first to speak of sarcoma and carcinoma occurring together. He pointed out

that the origin of all sarcomas must be in the interstitial tissue. In 1879 also Rose collected nine sarcomas, one of which was a spindle-cell sarcoma according to the microscopical examination made by Professor Eberth. Heath, also in 1879, reported a spindle-cell sarcoma in which "no trace of the original structure of the thyroid was to be found."

In 1881, Bircher collected sarcomas of the thyroid from the literature and found three spindle-cell sarcomas. In the same year Tillaux reported a spindle-cell sarcoma, giving detailed microscopical description. Wohlfler, in 1883, reported a fibro-sarcoma but in his report he described atypical epithelial proliferation that was of a carcinomatous nature. The same year Koch, speaking for himself and Demme, said sarcoma and carcinoma occurred together and that they could be differentiated only by the microscope and that the differentiation between them was of no practical value. In 1883, also, Braun tabulated the sarcomas of the thyroid from the literature and found spindle-cell sarcomas reported by Czerny, Kaufmann and Sonnenberg. He himself reported one spindle-cell sarcoma. Two years later Rotter collected malignant tumors of the thyroid and added a mixed round-cell and spindle-cell sarcoma. Bowlby in 1885, also, reported a fibro-sarcoma of the thyroid, stating that sections taken from the periphery and the center were entirely fibrous without the least appearance of either alveolation or of epithelial cells. In 1886 Moore reported a spindle-cell sarcoma of the thyroid. The pathological report states that in the portions examined no trace of the original gland tissue was found. The same year Kobler reported a spindle-cell sarcoma with "a partially alveolar structure." In 1887 Shattuck, and in 1888 Ploennis, Jones and Battle reported spindle-cell sarcomas of the thyroid. In 1889 Orcel included two spindle-cell sarcomas in his series of malignant tumors of the thyroid, one of Frerich's and one of his own. In 1891, Roux added a fibro-sarcoma to his list of reported cases. In 1897, Rabé reported a mixed round-cell and spindle-cell sarcoma that Ehrhardt later cites as a spindle-cell sarcoma. The same year Reverdin and Buscarlet reported a spindle-cell sarcoma of the thyroid. In 1897 also, Tiffany and

Lanier collected fifteen sarcomas of the thyroid and of these seven were spindle-cell sarcomas, one of which was their own case. In 1898 Limacher made an exhaustive study of spindle-cell sarcomas and concluded that the tumor cells were related to the blood-vessels in his cases. In the same year Kummer reported a thyroid tumor showing both carcinomatous and typical sarcomatous spindle-cells.

In 1899, Morf collected forty sarcomas of the thyroid, six of which were spindle-cell, three fibro-sarcomas and seven of the mixed-cell type. The same year Ewald reviewed sarcoma of the thyroid and stated that spindle-cell sarcomas do occur. In 1899 also, Schiller reported three spindle-cell sarcomas from the Heidelberg surgical clinic. Firth in England, the same year, reported a tumor of the thyroid that is later referred to by Ehrhardt as a spindle-cell sarcoma. Also in 1899, Cumston reported a spindle-cell sarcoma. Lartigau in 1901 added fifteen sarcomas to the forty collected by Morf three years previously. He stated that spindle-cell, round and mixed-cell tumors are the most common. In 1902 Ehrhardt cited seventeen spindle-cell and seven fibro-sarcomas found in the literature and remarked that fibro-sarcomata are difficult to distinguish from scirrhus carcinoma. In 1904 Papin and Saborianu reported a typical sarcoma made up of spindle-cells, the thyroid tissue represented only by a thin layer of cells pressed against the periphery. Saltykow in 1905 reported a typical spindle-cell sarcoma in the left lobe of the thyroid and a mixture of carcinoma and sarcoma in the right lobe and refers to the similarity of the cases reported by Ehrhardt, Kaufmann, Kummer and Woelfler.

Mueller and Speese in 1906 added eighteen sarcomas to Ehrhardt's list, making a total of one hundred eighteen, of which thirty were spindle-cell or fibro-sarcomas, among them a spindle-cell sarcoma of their own. The description of their tumor closely follows Kaufmann. Kocher in 1907 reported forty-six malignant tumors of the thyroid and made the illuminating statement that all but one of these proved to be of a carcinomatous nature although in some cases the tumor was supposed at first to be a spindle-cell sarcoma until careful examination revealed its epithe-

lial nature. He also described carcinoma and sarcoma occurring together. In the same year Herrenschmidt reported a spindle-cell sarcoma, saying it also showed alveolation suggesting epithelium and nodules of true epithelioma. Also in 1907, Vanderveer reported a fibro-sarcoma. In 1908, Williams reported one case of sarcoma of the thyroid, type cell not given. He is very emphatic in stating that sarcoma and carcinoma occur together but that transitions from one to the other have no existence, Virchow to the contrary, notwithstanding. In 1909 Michel reported spindle-cell sarcoma and carcinoma in the same tumor. Chambers in the same year collected the sarcomas of the thyroid found at the Royal Free Middlesex Hospital in a period of ten years and of these four were spindle-cell sarcomas. The author stated that these sarcomas are similar in structure to sarcomata occurring in other organs. In 1913 Porter added five sarcomas to those previously reported by Mueller and Speese, one a fibro-sarcoma and his own case which was "undoubtedly a spindle-cell sarcoma" according to the pathologist. Also in 1913 Wissmer-Kovarsky, directed by Professor Askanazy, reviewed the reported cases of malignant tumors of the thyroid gland. She noted that histological classifications do not agree, expressing regret that Langhans did not clear up the difficulty. She cited three spindle-cell sarcomas, only one of which had the classical appearance of sarcoma without a trace of epithelial cells. She indicated her skepticism by propounding the question, "Is there such a thing as sarco-carcinoma?"

In 1917 Crotti reviewed the literature in preparation for a paper on malignant goitre and made the statement that a differential diagnosis between carcinoma and sarcoma is evidently not easy. His observations were chiefly clinical. In 1917 also, Vandenberg described a case of spindle-cell sarcoma of the thyroid. The microscopical description was by Professor Warthin. Binnie in 1918 complained that the histological description of malignant tumors of the thyroid is most confusing. He reported a spindle-cell sarcoma. The histological examination was made by Professor Welch. In 1919 Kreglinger reported one case from the Hanover Hospital which he designated as a typical spindle-

cell sarcoma. In the same year Simpson reported the malignant tumors of the thyroid found in the New York State Hospital at Buffalo and stated that the sarcomas are usually of the spindle-cell variety. Von Rijssl in 1920 reported a mixed round-cell and spindle-cell sarcoma. Also in 1920, Bouman reviewed the literature and found one hundred eighty carcinomas to one hundred ten sarcomas. He made no attempt to classify them except clinically. However, he did mention fibro-sarcoma. It is noticeable that the authors of the significant reviews in American literature give little attention to the histology of sarcoma of the thyroid.

In 1920, Berry reported two sarcomas of the thyroid without microscopic description. In 1907 he had reported a spindle-cell sarcoma and in 1901 three spindle-cell sarcomas, one of which was his own case. This case was cited by Ehrhardt in 1902.

In 1921 Wilson reviewed the literature of malignant tumors of the thyroid, reported since 1914, and discussed the sarcomas observed at the Mayo Clinic together with those reported to him by personal correspondence from sixty-seven American surgeons. According to Wilson's view, spindle-cell sarcoma is the most common type of sarcoma of the thyroid gland and such tumors almost invariably contain large or small groups of parenchymatous (epithelial) cells which are also proliferating. He has reported nineteen sarcomas, ten of which are classified, including among them tumors designated as carcino-sarcoma, adeno-sarcoma and one spindle-cell sarcoma. He has stated that we must continue to call these tumors sarcomas whatever may be our hypothesis with regard to their epithelial or mixed origin.

Speese and Brown, in 1921 also, reported nineteen carcinomas and three sarcomas of the thyroid, without classifying the latter. In this report they mentioned the occurrence of carcinoma with sarcoma.

In Table 1 is shown the chronological list of reports of carcinoma, sarcoma and spindle-cell sarcoma.

The earlier reports are unconvincing. It would appear, however, that there are reports of six fibroblastic sarcomata which

cannot be thus dismissed, namely, those reported by Heath, Tillaux, Bowlby, Moore, Porter and Kreglinger, while those by Vandenberg and Binnie seem to be authentic.

TABLE I

Malignant Tumors of the Thyroid Gland

Reported by various authors, classed as carcinoma and sarcoma and as spindle-cell sarcoma

| Year | Author | Carcinoma | Sarcoma | |
|-----------|----------------------|-----------|---------|--------------|
| | | | Total | Spindle-cell |
| 1860..... | Foerster | 4 | 3 | 1 |
| 1871..... | Muller | | 1 | 1 |
| 1876..... | Doleris | | 1 | 1 |
| 1876..... | Socin | | 1 | 1 |
| 1879..... | Rose | 9 | 4 | 1 |
| 1879..... | Kaufmann (lit.) | 12 | 3 | 2 |
| | Kaufmann (own) | 11 | 3 | 1 |
| 1879..... | Heath | | 1 | 1 |
| 1880..... | Maas | | 1 | 1 |
| 1881..... | Bircher | | 8 | 3 |
| 1881..... | Tillaux | | 1 | 1 |
| 1883..... | Wolfler | | 5 | 1 |
| 1883..... | Braun (lit.) | 51 | 12 | 2 |
| | Braun (own) | 3 | 4 | 1 |
| 1885..... | Rotter (lit.) | 13 | 3 | ? |
| | Rotter (own) | 5 | 1 | 1 |
| 1886..... | Bowlby | | 1 | 1 |
| 1886..... | Moore | | 1 | 1 |
| 1886..... | Kobler | | 1 | 1 |
| 1887..... | Shattuck | | 1 | 1 |
| 1889..... | Orcel | 11 | 5 | 3 |
| 1891..... | Roux | 3 | 4 | 1 |
| 1892..... | Pick | | 1 | 1 |
| 1897..... | Rabé | | 1 | 1 |
| 1897..... | Reverdin & Buscarlet | | 1 | 1 |
| 1897..... | Tiffany & Lanier | | 15 | 7 |
| 1898..... | Limacher | 38 | 44 | ? |
| 1898..... | Kummer | | 1 | 1 |
| 1899..... | Morf | | 40 | 6 |
| 1899..... | Ewald | ? | ? | ? |
| 1899..... | Schiller | 3 | 23 | 3 |
| 1899..... | Firth | | 1 | 1 |
| 1899..... | Cumston | | 1 | 1 |
| 1901..... | Lartigau | | 15 | ? |

As another addition to this list, the following case is presented:

The patient, Lydia Magnarello, a girl of sixteen years, was admitted to the New York Post-Graduate Hospital, February 25, 1921, service of Dr.

Moorhead. The family history was negative, and the patient had always been a healthy girl except for the present illness.

TABLE I (Continued)

Malignant Tumors of the Thyroid Gland

Reported by various authors, classed as carcinoma and sarcoma and as spindle-cell sarcoma

| Year | Author | Carcinoma | Sarcoma | |
|-----------|-------------------|-----------|---------|--------------|
| | | | Total | Spindle-cell |
| 1901..... | Carrell | 80 | 3 | ? |
| 1901..... | Berry | 13 | 20 | 1 |
| 1902..... | Ehrhardt | 150 | 99 | 17 |
| 1904..... | Papin & Sabareanu | | 1 | 1 |
| 1905..... | Saltykow | | 1 | 1(?) |
| 1906..... | Muller & Speese | 181 | 188 | 30 |
| 1907..... | Langhans | ? | 1 | 1(?) |
| 1907..... | Kocher | 44 | 1 | 1 |
| 1907..... | Herrenschmidt | | 1 | 1 |
| 1907..... | Berry | 5 | 2 | 1 |
| 1907..... | Vanderveer | | 1 | 1 |
| 1909..... | Michel | | 1 | 1 |
| 1909..... | Chambers | 15 | 8 | 4 |
| 1913..... | Porter | | 5 | 1 |
| 1913..... | Wissmer-Kovarsky | | 10 | 3 |
| | (Chiari) | 11 | 5 | |
| | (Hedinger) | | 7 | 6(?) |
| 1914..... | Wissmer-Kovarsky | 29 | 10 | 4 |
| 1917..... | Crotti | ? | ? | ? |
| 1917..... | Vandenberg | | 1 | 1 |
| 1917..... | Judd | 105 | 6 | ? |
| 1918..... | Binnie | | 1 | 1 |
| 1919..... | Kreglinger | | 1 | 1 |
| 1919..... | Simpson | | ? | ? |
| 1920..... | Von Rijssel | | 1 | 1 |
| 1920..... | Bouman | 180 | 110 | ? |
| 1921..... | Berry | 12 | 2 | ? |
| 1921..... | Wilson (U. S.) | 98 | 19 | |
| | (Mayo) | 115 | 19 | 1 + |
| | (lit.) | 524 | 39 | |
| 1921..... | Speese & Brown | 25 | 3 | |

About January, 1919, the patient noticed an enlargement of the neck in the median anterior aspect. This increased rapidly in size, extending toward the right side. She was operated upon in June, 1920, about eighteen months after first noticing the tumor. The operation was not completed owing to the excessive hemorrhage. Only a small amount of tissue was removed which was not examined microscopically. At the time of admission to the Post-Graduate Hospital, February 25, 1921, the tumor was larger than before the attempted operation and more irregular in outline. There were no symptoms except those referable to the mechanical effect of the tumor.

TABLE 2

Spindle-cell Sarcomas Reported by Various Authors

Showing recognized presence of epithelial cells and inclusion of histological details in the reports. Where histological details are given this is indicated by + mark.

| | Sarcoma | Epithelial Cells | Spindle Cells | Histological Details |
|---------------------------|---------|---------------------|------------------|-------------------------|
| Foerster..... | I | + | + | + |
| Foerster..... | I | + | + | |
| Foerster..... | I | + | + | |
| Muller..... | I | ? | + | + |
| Doleris..... | I | ? | + | |
| Socin..... | I | ? | + | |
| Rose..... | I | ? | + | + Eberth |
| Kaufman..... | I | + | + | + |
| Heath..... | I | None | + | + |
| Maas..... | I | ? | + | Mixed cells |
| Tillaux..... | I | None | + | + |
| Wolfler..... | I | + | + | |
| Koch..... | I | + | + | |
| Braun..... | I | . | + | Mixed cells |
| Braun..... | I | | + | Mixed cells |
| Braun..... | I | | + | Mixed cells |
| Bowlby..... | I | None | + | + |
| Moore..... | I | None | + | + |
| Kobler..... | I | + | + | |
| Shattuck..... | I | ? | + | |
| Plonnis..... | I | ? | + | |
| Jones & Battle..... | I | ? | + | |
| Orcel..... | I | ? | + | |
| Frerichs..... | I | ? | + | |
| Roux..... | I | ? | + | Niehus |
| Pick..... | I | | + | Secondary |
| Rabé..... | I | ? | + | Mixed cells |
| Reverdin & Buscarlet..... | I | + | + | + |
| Tiffany & Lanier..... | I | + | + | + |
| Kummer..... | I | + | + | |
| Morf..... | I | + | + | Mixed cells |
| Schiller..... | I | ? | + | |
| Schiller..... | I | ? | + | |
| Schiller..... | I | ? | + | |
| Firth..... | I | + | + | Mixed cells |
| Cumston..... | I | + | + | |
| Rotter..... | I | + | + | |
| Lartigau..... | I | + | + | |
| Papin & Saborianu..... | I | + | + | |
| Saltykow..... | I | + | + | |
| Ehrhardt..... | I | + | + | |
| Muller & Speese..... | I | + | + | |
| Kocher..... | I | + | + | |
| Herrenschmidt..... | I | + | + | |
| Michel..... | I | + | + | |
| Porter..... | I | None | + | + |
| Wissmer-Kovarsky..... | I | ? | + | + |
| Kovarsky..... | I | + | + | |
| Kovarsky..... | I | + | + | |
| Vandenberg..... | I | | + | + Warthin |
| Binnie..... | I | | + | + Welch |
| Kreglinger..... | I | None | + | + |
| Von Rijssel..... | I | ? | + | Mixed cells |
| Berry..... | I | ? | + | |
| Mallory..... | I | + | + | |

Physical examination was negative except for the tumor of the neck. There was a tumor mass involving the entire right side of the neck extending from the angle of the jaw along the mandible two inches beyond the median line, overlapping the clavicle below and posterior to the anterior border of the trapezius muscle. The tumor was irregularly nodular and resilient. It was not attached to the skin. The skin over it was bluish in color with dilated veins. A pre-operative diagnosis of colloid goitre was made.

FIG. 1. Spindle-cell fibroblastic sarcoma of the thyroid gland. The structure of the tumor everywhere conforms to this type. Photograph of section stained with hematoxylin eosin.

Radiographic examination showed a large tumor in the soft structures in the right cervical region, of diffuse, even density without apparent bony attachment.

On March 3, the tumor was removed by Dr. Moorhead, the posterior capsule remaining. The operation lasted one hour and five minutes. The patient died ten hours later. Post-operative diagnosis was colloid goitre.

Tissue received at Laboratory was put in ten per cent. formalin solution. Later some of the pieces were transferred to Zenker's solution.

FIG. 2. Spindle-cell fibroblastic sarcoma of the thyroid gland. Photograph of a section stained with Mallory's connective-tissue stain.

Gross description: There are about twenty irregular fragments of fairly firm, pale grey tissue, total weight 255 grams. The largest pieces are 6 to 7 cm. in diameter. A few pieces are covered with a thin capsule, beneath which there are numerous irregular hemorrhagic areas. The tissue is somewhat brittle. The broken surfaces are coarsely serrated, the serrations suggesting coarse bundles of fibrous tissue. The cut surface is smooth and glistening, marked throughout by interlacing white fibre bundles separated by translucent streaks. There is nothing to suggest thyroid gland or colloid material.

Microscopic: Sections taken from many areas are identical in histological structure. They show sheets of fusiform cells closely packed. The cells are arranged in bundles several millimeters in diameter and appear in longitudinal, transverse and oblique sections. The bundles are separated by con-

nective tissue fibrils. The cell nuclei are generally fusiform in longitudinal and round in transverse section. The average diameter is about twice that of a red blood cell and the length two to five times the diameter. The cell body is relatively small and stains faintly. The nuclei vary in staining prop-

FIG. 3. Spindle-cell fibroblastic sarcoma of the thyroid gland. Intercellular fibrils are stained intensely black. Photograph of a section stained by the Maresch-Bielchowsky method.

erties; some are pale and vesicular and a few are pyknotic and compact. Occasionally mitotic figures are seen, but not in all oil-immersion fields. Usually one, but rarely four may be seen in a single field. The spaces between the cells are sometimes less and sometimes more than the cell diameters and are crossed by both coarse and fine fibrils. The blood supply is abundant in a few areas. The blood vessels appear for the most part as narrow branching channels between the cell bundles and as minute tubes between the cells. The channels are occasionally without definite walls and red blood cells are seen between the adjacent tumor cells. (See Fig. 5.)

The interest centers upon the fibrils between the tumor cells. With hematoxylin and eosin the fibrils are stained pink. With Van Gieson's stain they are pink and of the same nature as those forming the delicate walls of the blood channels, but areas having no blood channels show the fibrils between

FIG. 4. Spindle-cell fibroblastic sarcoma of the thyroid gland. Inter-cellular fibrils are stained intensely black and nuclei are very indistinct. Photograph of a section stained by the Maresch-Bielchowsky method.

the cells. With Mallory's connective tissue stain the intercellular fibrils stain blue. In some areas they are numerous and between all the cells, but in other areas they are less plentiful, even scarce. There are also delicate red fibrils attached to the cells. Some cell bodies are opaque and stained diffusely bright blue, others are diffusely bright red. (See Figs. 2 and 5.)

With Maresch's modification of the Bielchowsky stain these fibrils stain intensely black and conform exactly to Kuro's description of connective tissue fibres as he demonstrated them for the identification of tumor cells. (See Figs. 3, 4 and 6.) With Weigert's resorcin-fuchsin stain, elastic fibres are not found in the sections except in the walls of the largest blood channels.

FIG. 5. Spindle-cell fibroblastic sarcoma of the thyroid gland. Intercellular fibrils are blue. Drawing with Zeiss objective 2 mm. Compensation-Ocular 6. Section stained with Mallory's connective-tissue stain.

In no section have we found epithelial cells and nothing to suggest alveolar arrangement. No colloid has been found.

We have attempted by the use of several staining methods, hematoxylin and eosin and Van Gieson, supplemented by those of Mallory and Bielchowsky, to demonstrate that the intercellular fibrils of this tumor are of connective tissue origin and that the spindle-cells of this tumor are of the same derivation. All stains of the tumor sections have been made with control sections of known tissue on the same slide and it seems reasonable to assume that the results may be depended upon as technically correct.

CONCLUSIONS

Most authors agree that the clinical aspect and gross appearance are not diagnostic of sarcoma of the thyroid gland and that the differentiation from carcinoma must be made by the microscope. Tumors without this examination cannot be accepted as sarcomas.

FIG. 6. Spindle-cell fibroblastic sarcoma of the thyroid gland. Inter-cellular fibrils are black. Drawing with Zeiss objective 2 mm. Compensation-Ocular 6. Section stained by Maresch-Bielchowsky method.

From the microscopic evidence there are possibly six reported cases of spindle-cell sarcoma of the thyroid gland of which two, namely, the tumor reported by Vandenberg and examined by Warthin and that reported by Binnie and examined by Welch, seem to be definitely established.

The necessary requirements for a positive diagnosis of spindle-cell sarcoma of the thyroid are the same as for diagnosis of sarcoma in any other locality. All sarcomas should show inter-cellular connective tissue fibrils, and tumors not conforming exactly to these requirements are not true sarcomas and should not be so designated.

The tumor reported here conforms to these requirements and is, therefore, a true spindle-cell fibroblastic sarcoma of the thyroid gland.

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Discussion:

DR. LARKIN: I was very much interested in the presentation of primary tumors of the thyroid. The completeness of the report is only to be appreciated by those who have had ample opportunity to look over tumors of this particular type. The very exhaustive manner in which Dr. Meeker has presented this subject is amazing, and leads us to the conclusion that the final

diagnosis and differentiation of tumors of the thyroid is only to be made by the microscope. One of the slides looked like the tumor which was reported by Lartigau several years ago, and at that time the observation was made that they were of a definite type and belonged to the spindle-celled variety. We are wont to look at tumors of the thyroid, and dismiss them as colloid goiters, and I think a more extensive study should be made of these tumors which are dismissed by pathologists as belonging to the ordinary type of adenocarcinoma. The presentation is certainly a very excellent one from the standpoint of the differentiation of tumors of the spindle-cell variety in the thyroid gland.

DR. EWING: Confronted by this formidable list of authorities cited, and especially by the very thorough and convincing study of Dr. Meeker's case, there would seem to be little ground remaining for the statement that the existence of primary sarcoma of the thyroid remains to be demonstrated. Certainly one must admit that if there is a primary sarcoma of the thyroid, her case is one, if not the first one, fully proven.

However, there is always a defensive argument even in the most hopeless situations. It may be pointed out that the earlier authors cited were all positive about their diagnoses of sarcoma; later ones were not quite so sure, one critical observer concluding merely that there are sarcomas of the thyroid. Recently one finds more frequent admissions that the differential diagnosis between sarcoma and carcinoma is very difficult in the thyroid, and an increasing number of mixed sarcomas and carcinomas is mentioned, which shows that the study of tumors of the thyroid has become more critical. Now this story reflects my own experience with sarcoma of the thyroid. Some years ago I saw Lartigau's case, and was not satisfied that it was true sarcoma on account of the presence of certain cells which seemed to be epithelial. It was at least a carcino-sarcoma. In so many cases of apparent sarcoma of the thyroid I have found areas of polyhedral cells and transitions of polyhedral epithelial cells into spindle-cells, that I have become quite skeptical regarding the usual diagnosis of sarcoma in this organ. It seems quite certain that no one should venture the diagnosis of sarcoma of the thyroid without considerable search for areas of epithelial cells, since in tumors of this gland epithelial tumor cells are particularly prone to assume a spindle form.

Moreover, I think the time is passed when one can assert that a tumor is a mesoblastic sarcoma simply because it presents spindle cells. Not even the demonstration of various intercellular fibrils will suffice for this purpose. One must offer in addition some evidence regarding the histogenesis of the tumor, such as we have for periosteal and neurogenic sarcoma. Such evidence is not available for sarcoma of the thyroid. Yet one cannot presume that the connective tissue of the thyroid gland is immune to malignant tumor growth. Sarcomas probably arise in this gland as in others, but the general pathology of the thyroid does not reveal the same satisfactory basis for recognition of sarcoma as in many other situations. Until some one in a series of cases can trace the histogenesis of sarcoma of the thyroid I think the final proof of the existence of such a tumor is wanting. This proof has been fur-

nished for many other sarcomas, and the thyroid need be no exception.

In the case of Dr. Meeker's tumor I had the opportunity to study the sections. We could find no trace of epithelial cells in many sections, but I was struck with the resemblance of the histological picture to that of neurogenic sarcoma, with intertwining fibrils, and having no better resort in an embarrassing situation, I ventured to suggest that it was a neurogenic sarcoma arising from the nerve structures of the gland.

There is one particular group of so-called sarcomas of the thyroid, probably figuring in the literature, which seem to have no relation to true mesoblastic sarcomas. These are the various stages of sclerosis exhibited by Riedel's "iron-hard struma," cellular stages of which I believe are described by Hashimoto (Langenbeck's *Archiv*, xcvii, 219). These cases seem to represent cellular and sclerosing stages of a benign lympho-granuloma of the thyroid. I have seen both phases in the same tumor. They may greatly resemble a sarcoma but have nothing to do with true mesoblastic sarcoma.

Therefore, while Dr. Meeker has succeeded admirably in demonstrating a sarcoma in the thyroid gland, I must continue to feel that until the matter of histogenesis has been cleared up, the existence of a true mesoblastic sarcoma arising from the connective tissue of the thyroid gland remains uncertain.

DR. MEEKER: I wish to emphasize that many sections were taken; more than a hundred sections were stained, and we have found no evidence of epithelial cells. I would like to ask Dr. Ewing what further steps are necessary in this demonstration, and ask him to suggest what I should do next.

DR. EWING: I do not think one can do anything more with this case. This is the best observation recorded which deserves consideration as a primary sarcoma of the thyroid. It may however be a neurogenic sarcoma. The histogenesis of a tumor cannot be demonstrated on a single case. One has to lay a foundation for sarcomatous processes in the thyroid from the general pathology of the gland, and then one has to collect a series of tumors from which one can demonstrate the beginnings of the tumor in one structure. That is the nature of much of the study of tumors that is going on today.

The importance of such studies is revealed in the fact that where the histogenesis of a group of tumors has been determined, as of neurogenic or osteogenic sarcoma, it usually transpires that the tumors thus identified show specific etiological, histological, and clinical features, which render them specific neoplastic diseases.

DR. MEEKER: I want to make it clear that I did not intend in any way to oppose Dr. Warthin and Dr. Welch to Dr. Ewing.

THE COLORIMETRIC DETERMINATION OF THE HYDROGEN ION CONCENTRATION

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The importance of a knowledge of the hydrogen ion concentration of various biological fluids such as urine, blood, bacteriological culture media, etc., has come to be quite generally appreciated. The difficulties encountered in making the determination, however, have restricted its use to specially equipped laboratories. The electrometric methods still require expensive apparatus and special training, but the colorimetric method has been greatly improved and simplified, especially at the hands of Sørensen and Clark. With this method, as generally employed, a series of tubes are made up containing buffer solutions with pH differences of 0.2 for the range of the indicator. These are employed for comparison with the unknown. Obviously the preparation of such a series of standards is time-consuming and their use rather cumbersome.

It has previously been pointed out¹ that with the use of two wedges in a modified Hellige colorimeter, it is possible to obtain all the shades of color in a given indicator from the acid to the alkaline side, when one wedge is filled with an acid solution of the dye and the other with an alkaline solution. These may be made with buffer solutions of a definite pH, or as we have recently observed, of solutions of the indicator made sufficiently acid or alkaline to produce a complete change in the color of the indicator. Obviously it is essential that the concentration of indicator should be the same in both standard and unknown. Where it is desired to read very small differences in pH over only a limited range it is best to make the standards of a definite pH just outside of the range to be covered. With this technic it is possible to make readings which are accurate to a difference of roughly \pm pH 0.02.

Barnett and Barnett² and Gillespie³ have employed similar

principles in the colorimetric measurement of the hydrogen ion concentration. The former authors employ a low, narrow, rectangular glass box having a diagonal glass partition, one being used for the acid and the other for the alkaline solution of the indicator, while the latter achieves the same result by having a small movable cup fitted over the plunger but inside the cup of a Duboscq type colorimeter.

The use of wedges which are individually movable provides a much more flexible system.⁴ The reading of the wedge containing the dominant color of the dye, *e.g.*, the red in phenol red, characterizes the hydrogen ion concentration, the yellow wedge being employed simply to obtain a correct color match. This being the case it may also be employed to correct for any slight error due to extraneous yellow pigment in the unknown.

At the author's suggestion E. Leitz, New York, has constructed a new wedge colorimeter for these determinations. Briefly the instrument comprises a brass box 30 cm. in height, containing a rack and pinion arrangement for three wedges, the movement of the wedges being entirely within the closed box. Readings are taken from 100 mm. scales which emerge from the top of the instrument as the wedges are raised. The instrument is provided with prisms and an eyepiece in front and a milk-glass plate in back for the entrance of light. For the latter a small lamp box may be substituted. A door at the side gives access to the wedges and to the cup for the unknown which is mounted on it. Two wedges provide for biocolorimetric work as in the pH determination. However, to obtain a perfect match with unknown solutions which are slightly turbid or colored a third wedge may be used.

Since giving a preliminary description of this instrument,⁴ it has been improved by the replacement of the Helmholtz prisms with the type of prisms employed in instruments made on the Duboscq pattern. Thus modified the light passes more nearly through the center of the wedges and cup, furnishing a better field for comparison. The lamp box as now constructed uses only reflected light, which passes through a very thick daylight glass. The small nitrogen bulb is set below the field of vision,

the reflecting surface being covered with aluminum paint. The light obtained from the present lamp is quite equal to daylight in quality, and superior to it in intensity.

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CHEMICAL CHANGES IN THE BLOOD IN PNEUMONIA

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It is a fact of common knowledge that the development of pneumonia in human subjects entails a more or less severe impairment of renal function. That this disturbance of kidney efficiency cannot be attributed to a direct transfer of the infection to the kidneys is evident from studies upon the urine. With the object of determining the mode of production of this renal impairment and its prognostic significance, the study of the chemical changes in the blood was made in a series of fifty cases of pneumonia of various types. An attempt was made to obtain the blood specimens at frequent intervals throughout the course of the disease, but in the majority of cases this proved impossible, since the patients did not enter the hospital until the pneumonia was well advanced. The observations made include determinations of the nonprotein and urea nitrogen, uric acid, creatinine, sugar and chlorides of the whole blood, and the carbon dioxide combining power of the blood plasma.

It was noted that about the time of the crisis the nonprotein nitrogen was definitely increased from 34 to 156 mg. per 100 c.c. This increased nonprotein nitrogen was found to be due to a rise in the undetermined fraction, and apparently was caused by an accumulation of complex protein catabolites producing

a toxemia. This toxemia resulted in a damage to kidney function. Following the increase in the nonprotein nitrogen the uric acid concentration of the blood rose from 3.8 to 11 mg., and subsequently there was a rise in the urea nitrogen to 20 mg. or more. When the urea nitrogen had reached this level a definite accumulation of creatinine was noted. In a few instances the creatinine exceeded 5 mg. per 100 c.c., and death in these cases could undoubtedly be attributed to the severe impairment of renal function. The order of retention in the blood of the nitrogenous waste products was analogous to that observed in nephritis of the interstitial type, first, the uric acid, secondly, the urea, and finally, the creatinine. Although the secondary kidney damage may not be the only cause of death in pneumonia, it may be said that the prognosis from the standpoint of renal function becomes grave when the urea nitrogen of the blood exceeds 25 mg. per 100 c.c.

The normal concentration of the chlorides of the whole blood varies from 0.45 to 0.50 per cent. (as NaCl). A significant decrease in the blood chlorides from 0.288 to 0.425 per cent. was found in the majority of the patients before the crisis. It was not possible to establish any definite relation between the decrease in the blood chlorides and any of the clinical manifestations of the disease. At the time of the crisis, the chlorides quickly rose to a level exceeding 0.50 per cent., and gradually dropped back to within normal limits. In a few cases subnormal blood chlorides were found with a retention of the nitrogenous waste products.

Pneumonia was found to produce a slight decrease in the carbon dioxide combining power, 45 to 50 volumes per cent. This apparent mild acidosis is no doubt due to a deficient elimination of carbon dioxide by the lungs. However, when the blood showed a marked accumulation of the nitrogenous waste products, the carbon dioxide combining power was found to be diminished to 20 to 30 volumes per cent.

COMPATIBILITY OF BLOOD FOR TRANSFUSION

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The knowledge of isohemagglutinins and isohemolysins is not of recent date. In 1901 Landsteiner¹ divided the human race into three groups according to the action of their serums and cells when brought into contact. Group I comprised all individuals whose cells were agglutinated by no serums and whose serums agglutinated all other cells. Group II was made up of those whose cells were agglutinated by serums of Groups I and III, and whose serums agglutinated cells of Group III. In Group III were placed those whose cells were agglutinated by serums of Group I and II and whose serums agglutinated cells of Group II. It was not until 1907 that Jansky² announced the recognition of still one more group, which he called Group IV, composed of a very limited number of people, whose cells were agglutinated by all other serums and whose serums agglutinated no cells. The designation of human blood groups as above defined is now known as the Jansky classification.

Moss in 1910 and 1911 confirmed these findings and reported that pathologic as well as normal blood could be classified into four groups. Unfortunately Moss interchanged Groups I and IV of Jansky's classification so that the Jansky Group IV is the Moss Group I and Jansky Group I is Moss Group IV. Thus there are two classifications in use at this time, though the Jansky classification has been adopted by the American Association of Immunologists and the American Association of Pathologists and Bacteriologists and would appear to be the logical choice.

With known serums of Group II and Group III it is a very simple matter to group all individuals. A drop of serum II is put on one end of a glass slide and a drop of serum III on the other end. A drop of blood of the person to be tested is mixed with the different serums. Usually any agglutination is visible

to the naked eye, but the preparation should always be examined with the low power of the microscope.

Cells of different individuals differ markedly in the amount of agglutinin they contain. Likewise serums also vary in agglutinating power, some being quite low in their agglutinin content. It can thus be seen that for correct grouping, it is essential to select for standard test serums, those with strong agglutinating power. To ten parts of serum is added one part of 10 per cent. sodium citrate in 0.9 per cent. salt solution and one part of 5 per cent. carbolic acid and the final product put up in sealed ampoules. It keeps its agglutinating properties for many months.

In those cases that come up for transfusion, if time permits, a mutual compatibility test should be done. This is done by obtaining 4 or 5 cubic centimeters of defibrinated blood from both patient and selected donor. The cells and serum are separated, the cells washed and a 1:20 suspension in salt solution made of each. Six small tubes are set up. Into each of the first three is placed 0.1 c.c. of the donor's red blood cell suspension; into the next three a similar amount of patient's red blood cell suspension; into the first and fifth tubes 0.4 c.c. of the patient's serum, and to the second and fourth 0.4 c.c. of the donor's serum. All the tubes are made up to the volume of 1 c.c. with 0.9 per cent. salt solution. These tubes are shaken and incubated for two hours at 37° C. and let stand at room temperature over night, which insures a more even setting of the cells than in the ice box. The readings taken on the tubes are for agglutination and hemolysis. Usually within one half to one hour after incubation the test can be read for agglutination. This test serves as a check upon the grouping and assures the patient of a compatible donor, as incompatibilities within the group, although infrequent, do nevertheless occur.

Only two such incompatibilities within the group have been met with in our mutual compatibility tests, both in Group IV Jansky, one a young woman of twenty-one, and the other a child of four years. The young woman had pernicious anemia and at the time there was available only one donor of her group.

The donor's serum slightly hemolyzed the patient's cells. There was no apparent agglutination present in the tube. As this donor of her own group injured her cells less than donors of other groups and it seemed imperative that she be transfused, she was given 150 c.c. of blood. The subsequent reaction was very severe but not lethal and was followed by improvement.

In the case of the child only a grouping had been done and a professional donor called in. After 40 c.c. of blood had been given the transfusion was stopped on account of the condition of the patient. A request was then made for the mutual compatibility test with the donor used and in this test the patient's serum agglutinated and hemolyzed the donor's cells markedly. Another Group IV (Jansky) donor was found to be perfectly compatible.

One other case of interest has been met with, a pregnant woman who came into the hospital to be transfused on account of a pronounced anemia. This was her second pregnancy. During the first she was also very anemic and aborted about the fourth month, after which the anemia disappeared only to reappear during her second pregnancy. In this case grouping was not done, but mutual compatibility tests were done, trying out three brothers. All proved to be incompatible and furthermore the patient's serum was found to agglutinate her own cells. Her blood was then tested against bloods from donors of each group and found to be incompatible. No transfusion was done. At the end of the seventh month her red corpuscles had decreased to 800,000 per cu. mm. and miscarriage took place. Some months later she returned, apparently in good health. She had 3,500,000 red blood cells per cu. mm. and was found to belong in blood Group II.

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FATTY DEGENERATION OF THE HEART

A. M. MASTER, M.D.

The clinical and pathological diagnosis of "fatty heart" or of the heart the seat of "fatty degeneration"* is still too commonly made. A decade ago it was even more frequently diagnosed than it is now. Broadbent¹ described the etiology, symptoms, physical signs, prognosis and treatment of fatty degeneration of the heart. He says, "No form of heart disease is regarded with so much apprehension as fatty degeneration. More than any other, it causes with it the dangers of sudden death and the liability to angina pectoris."

Hirschfelder² also described the symptoms and signs of the heart of fatty degeneration. He says, "The most characteristic symptoms associated with the condition are those of general debility and feebleness, more or less languor and somnolence as a rule without marked cardio-respiratory symptoms except shortness of breath on exertion. The pulse is usually small, rather collapsing and feeble, the blood pressure is below normal . . . the pulse rate is increased. On physical examination the heart may be either normal or dilated, the sounds either feeble and distant or short and sharp, the apex impulse may or may not be well marked. The liver and spleen are often enlarged. There is sometimes edema of feet and ankles."

We are told that the tone of the cardiac muscle is diminished, that patients with fatty degeneration of the heart are very sensitive to digitalis and are frequently injured by it. Sudden death from overdose of this drug or from acute cardiac overstrain is more common in patients with fatty degeneration of the heart than in almost any other condition and finally spontaneous rupture of the heart is relatively frequent in this condition. And so pages have been written.

In summary, however, Hirschfelder frankly states that none

* We distinguish here between fatty degeneration of the heart with which this paper deals solely and fatty infiltration in which fat is present beneath the epicardium, or penetrates between muscle bundles even as far as the endocardium.

of the symptoms is "either constant or characteristic" and the diagnosis may have to be made by inference only. As Krehl³ says, there is no clinical sign for the diagnosis of fatty degeneration of the heart.

We believe that the clinical diagnosis of fatty degeneration should only be made on etiological grounds, *e.g.*, in phosphorus poisoning, pernicious anemia, etc., where we expect this finding. Otherwise to make this diagnosis during life is a very uncertain proceeding.

Having discussed fatty degeneration from the clinical aspect let us now look at the question from a pathological point of view. It is trite to state that necropsy findings must be in great part the criteria upon which diagnoses rest. Undoubtedly then, the frequency of the diagnosis of "fatty heart" is based upon the same frequency with which this type of heart is found on the post-mortem table. We are told by the highest authorities that fatty degeneration of the heart is a common pathological condition.

The etiology² is given as alcoholism, primary and secondary anemia, after hemorrhage, in association with myocarditis, valvular and other cardiac lesions, in most infectious diseases, in miners, smelters, and in many metal workers, etc.

Sir William Osler⁴ in discussing the anatomical basis of cardiac insufficiency says, "Fatty degeneration is a very common condition. It is found in the failing nutrition of old age, of wasting diseases and of cachectic states; in prolonged infectious fevers in which it may follow or accompany the parenchymatous changes. In pernicious anemia and in phosphorous poisoning the most extreme degrees are seen. . . . Lastly, in the hypertrophied ventricular wall in chronic heart disease fatty change is by no means infrequent. . . ."

"There appears to be a special proneness to fatty degeneration in the heart muscle which may perhaps be connected with its incessant activity."

It is our contention that the diagnosis of fatty degeneration of the heart is made too frequently in the pathological laboratory. Here the criterion of this condition is the presence of fat

within the muscle-cell. Adami says, "Fatty degeneration of the heart is a common condition characterized by the presence of minute globules of fat in the muscle fibers which are deposited in small droplets generally in line of the longitudinal fibrillæ of the cell." Years ago, then, from the work of Virchow,⁶ Adami⁵ and others we have all been taught that visible fat in the cardiac muscle cell was pathological, *i.e.*, fatty degeneration was present.

To prove our stand that fatty degeneration of the heart is diagnosed too often we decided to examine a series of pathological hearts and to utilize normal human hearts as controls.

For our pathological hearts we examined post-mortem the hearts of twelve patients from the medical services of Dr. L. A. Conner and Dr. W. L. Williams at the New York Hospital. These patients had been in the hospital as "cardiacs," *i.e.*, they were cases of myocardial or valvular disease or both, and the symptoms from which they suffered were primarily ascribed to their hearts. They all died with the classical symptoms of myocardial failure. The following is the clinical history typical of any one of these cases. The pathological findings in regard to presence or absence of fatty degeneration is also typical of all the hearts.

CASE 1. Chronic myocarditis. The patient, 57 years old, was admitted to the Hospital on March 3, 1921, and discharged on April 25, 1921. He entered the hospital complaining of dizziness, pain in abdomen and swelling of the legs. He gave a long history of alcoholism and for the past five years had dyspnoea on exertion and precordial pain, rarely with fainting attacks.

His heart was enlarged, 13 cm. to the left in the sixth space and 2 cm. to the right in the fourth space. The heart sounds were very poor in quality and distant, with extrasystoles. The rate was slow, 50 to 60.

The blood pressure was systolic 140, diastolic 90.

The urine showed a heavy trace of albumin, hyaline and granular casts, and specific gravity of 1.020.

The blood urea was 40 mg. per 100 c.c. of blood.

The autopsy findings were chronic parenchymatous nephritis, kidney infarcts, general atherosclerosis, chronic myocarditis (replacement fibrosis), hypertrophy of heart, congestion of liver, and chronic perisplenitis.

Gross examination of the heart showed on the surface of the organ a considerable increase of the fatty tissue. The heart was much enlarged. No areas of fibrosis were observed. The valves were negative, except for very slight thickening of the edge of the mitral valve. The coronaries were markedly thickened and calcified and narrowed throughout.

Microscopical examination of the heart revealed connective tissue replace-

ment in the region of the left apex and also in the right ventricle. The septum showed a moderate degree of fibrous replacement. There were a few small round cell foci at the pericardial surface of the left ventricle, and rarely in the muscle itself.

Innumerable fat droplets were found in large quantities in the muscle cells proper (see figure). These were arranged in the classically described positions for fatty degeneration, i.e., in longitudinal and transverse rows between the muscle fibrillæ and also areas of muscle cells filled with fat alternated with those practically free from this tissue.

FIG. 1. Case A. Ventricular septum. Scharlach R stain. Carmine Red fat droplets (black in microphotograph) in longitudinal rows between the fibrillæ of the muscle cell and arranged transversely (on either side of Krause's membrane).

Another modern writer⁷ who correlated the electrocardiographic findings during life with the pathological condition of

the cardiac muscle at death in describing five cases of heart failure reported, "Marked fatty degeneration" in each case! If one opens to any one of the well-known text-books^{8,9} in pathology he will find drawings and photographs illustrating fatty degeneration of the heart muscle which exactly duplicate the pictures we obtained in the hearts of every one of our series. Our Scharlach R

FIG. 2. Text-book illustration of fatty degeneration of the heart. (From Stengel and Fox: Text Book of Pathology, 1921, Ed. 7, p. 503.)

stain demonstrated the minute red droplets in every heart we examined. Previously we may have believed as other writers did that visible fat is pathological but when every heart depicted this finding our opinion was strengthened that this view was incorrect. Hence we had recourse to our series of controls. This is the crux of the matter. If the normal hearts evidenced no fat droplets in the muscle cell we could say that this finding

was pathological. However, if the controls showed fat granules in human cardiac muscle to be a normal finding then our entire conception of fatty degeneration of the heart would have to be revised, pathologically and clinically, because the latter depended for proof on the necropsy states.

Hence we obtained thirteen hearts at the Bellevue Morgue from individuals who had met sudden, violent death by bullet or stab wounds, etc., and who at autopsy showed no abnormality that was apparent to the unaided eye. These people ranged from eight to fifty-six years, the average age being thirty-two years. Sections were taken from each ventricle, septum and auricle. The tissue was fixed in formalin and within twenty-four hours

FIG. 3. Case D. Osmic acid stain. Results similar to Scharlach R (see Case A).

| Case No. | Age | Sex | Color | Cause of Death | State of Nutrition at Autopsy | Presence of Diffuse Red Fat Droplets in the Muscle Cell between the Fibrillæ arranged in Longitudinal and Transverse Rows | Presence of Golden Brown Pigment at the Poles of the Nuclei, <i>i.e.</i> , Pigment of Brown Atrophy |
|----------|-----|--------|-------|---|-------------------------------|---|---|
| A | 33 | Male | White | Blackjacked, <i>i.e.</i> , skull fracture, died within few hours | Good | Large quantity | Large quantity |
| B | 45 | Male | White | Stab wound of heart. Died immediately | Good | Slight or moderate amount | Large quantity |
| C | 45 | Male | White | Fracture cervical vertebræ. Died in few hours | Good | Present in some areas | Large, coarse, brown, bipolar pigment |
| D | 23 | Female | White | Cerebral hemorrhage died either immediately or within few hours | Very good | Abundance of granules | Good many granules |
| E | 40 | Male | White | Fracture of skull. Died in 3½ hours | Good | Abundance of granules | Good many granules |
| F | 31 | Female | White | Clinical diagnosis not made | Somewhat emaciated | Abundance of granules | Good many granules |
| G | 20 | Male | White | Shot to death. Died within 1 hour | Good | Very few granules | Good many granules |
| H | 42 | Male | White | Acute alcoholism | Good | Moderate amount | Very many granules |
| I | 32 | Female | Black | Died in few hours from hemorrhage after attempted criminal abortion | Good | Moderate amount | Very many granules |
| J | 34 | Female | Black | Acute alcoholism | Good | Great many granules | Very many granules |
| K | 56 | Male | White | Cerebral hemorrhage from blow | Good | Great many granules | Very many granules |
| L | 15 | Male | White | Shot to death. Died instantly | Good | Many granules | Moderate amount |
| M | 8 | Male | White | Run over by truck. Died in few hours | Good | Many granules | Moderate amount |

frozen sections were stained with a saturated solution of Scharlach R dye in equal parts of 70 per cent. alcohol and pure acetone. The technique followed was that given by Mallory and Wright.¹⁰ At the conclusion of the experiments we stained one of the hearts with osmic acid (formalinized material placed in Marchi's fluid and cut by the freezing microtome). The results obtained were similar to those with Scharlach R. In regard to the Scharlach R we found small red droplets of varying sizes in the sarcoplasm of the cardiac muscle cells. These were arranged in longitudinal and transverse rows, the longitudinal droplets appearing between myofibrillæ. The number of granules varied. Some hearts were stained diffusely and uniformly, some scarcely at all and commonly there were groups of cells which took the stain well while in the immediate vicinity were cells which contained little, if any, fat.

The so-called pigment of brown atrophy, which is located at the poles of the nucleus and is supposed to be an indication of senility of the muscle, was stained yellow, yellow-brown, or golden-brown with Scharlach R. At first we found it difficult to distinguish between it and the diffuse fat droplets but after some experience we were able, in practically every case, to differentiate between the coarser brownish bipolar granules and the smaller red fat droplets distributed diffusely throughout the cell and arranged in longitudinal and transverse rows. With osmic acid the bipolar pigment was stained light brown whereas the fat granules were intensely black.

Hofbauer¹¹ in 1905 described visible fat in normal human fetal muscle. Bell¹² in 1912 first showed that visible fat is normally present in the cardiac muscle of the common laboratory mammals.

He also demonstrated that the quantity of visible fat is increased when fatty foods are given and diminished when the animals are starved. Wegelin¹³ found fat in the cardiac tissue of rats. He also examined the heart of an insane man who had jumped out of the window and found fat in quantities, although the organs appeared to be normal at autopsy. He expressed the belief that fat could be demonstrated microscopically in normal human heart muscle. Eyselin¹⁴ of Berlin did not agree with this.

H. Hays Bullard¹⁵ in 1912 stated that although Scharlach R was not specific for neutral fat (Scharlach R and Sudan III stain neutral fats, fatty acids,

soaps and lipoids with varying degrees of intensity) and although he did not believe that all the colored droplets in mammalian cardiac muscle were neutral fat, yet he thought that most of them undoubtedly were.

In a subsequent communication Bullard¹⁶ showed that there is microscopically demonstrable fat in the normal cardiac tissue of rats, cats, dogs, hogs, oxen and sheep. More than two hundred animals were investigated. The fat droplets in the sarcoplasm were arranged in rows between the muscle fibrillæ and in transverse lines in segment J on either side of the membrane of Krause. He also noted fatty fibers side by side with non-fatty areas. However, in other cases all the cells showed a uniform diffuse mottled appearance.

We do not wish to go into detail of the histology and chemistry of fats. Those interested can obtain in detail the reason for the conclusion of Bullard. Bullard gave decisive evidence for believing that visible droplets of neutral fat occur in physiological circumstances in the cardiac muscle fibers of mammals. Space prevents the repetition of these arguments and proof.

(He utilizes a 20 per cent. solution of formalin¹⁷ rendered isotonic with 0.75 gm. NaCl per 100 c.c. liquid. Tissues are fixed for one half to five hours and then cut on the freezing microtome. If this procedure is followed the quantity of fat does not differ from that obtained in fresh tissues. By means of Herxheimer's alkaline alcoholic solution of Scharlach R fat may often be demonstrated in larger amounts than by the simple alcoholic solution of dye. (This stain¹⁸ is a saturated solution of Scharlach R in 70 per cent. alcohol to which 2 gm. of NaOH are added to every 100 c.c. of fluid. Precipitates must be avoided.)

Within the last few years several articles¹⁹ have appeared in the literature that tend to prove that the pigment of brown atrophy is an endogenous melanin and that some of the red droplets in the cell brought out by the Scharlach R are of exogenous lipochrome. But this lipochrome is stained a deep blue by Nile Blue Stain, not red,¹⁵ as the fat granules are. Other writers too, state that the pigment can be separated from the fat.

The presence of fat in the cells of normal human cardiac tissue was not only a revelation to us but to others. An eminent pathologist was shown our Scharlach R sections of normal hearts. Without knowing the history of the cases he stated that the hearts were pathological, *i.e.*, that they were in the condition of fatty degeneration. He was surprised indeed to learn that the sections were from normal human hearts.

It must be clear by this time that visible fat is a normal finding in human cardiac muscle. Similarly it must also be evident that visible fat within the muscle cell does not signify fatty degeneration.

Although we believe that fatty degeneration is quite rare in hearts of those dying from cardiac disease, localized areas of fatty degeneration in the heart muscle are not so uncommon. One of our twelve pathological hearts depicted this finding. (See figure.)

FIG. 4. Case A. Localized area of fatty degeneration in vicinity of infarcted heart muscle (low power microphotograph).

CASE 2. G. Coronary artery disease. The patient, 59 years of age, was admitted to the New York Hospital on May 25, 1921, and died June 7, 1921.

Sixteen months before entering the hospital the patient had a severe attack of abdominal gas pains. These recurred with increasing frequency with dyspnoea on exertion. Cough was present June 3, 1921. The pulse became irregular. The heart was enlarged slightly, and the sounds were distant. Clinically and from the electrocardiographic point of view the patient was considered to have coronary artery disease with thrombus formation. The blood pressure was systolic 110, and diastolic 70. The urine was normal. The Wassermann reaction was negative.

Gross examination of the heart showed that the organ was enlarged, weighing 500 gm. On the posterior surface of the left ventricle there was a pale focus. Three to four mm. beneath the endocardium there was a grayish yellow layer. The coronaries showed marked thickening; the lumen of the anterior descending branch of the left coronary was occluded by an old thrombus.

The microscopical examination revealed necrotic areas in the septum. Adjacent portions showed marked fatty degeneration as shown in sections stained with Scharlach R. There were areas of fibrous tissue replacement. In the lateral wall of the left ventricle there were also areas of fibrous replacement with less marked but very evident fatty degeneration and infiltration. The right ventricle appeared normal except for a slight increase of connective tissue. Here evidence of necrosis, fibrosis, nuclear changes, disappearance of muscle striations, great numbers of fat granules, etc., helped make the diagnosis of fatty degeneration of this localized area.

It appears therefore that in twelve hearts in which one might have diagnosed fatty degeneration of more or less severity not one showed this condition. This we proved on the basis of the normal hearts as a standard.

Certain facts must clearly be evident by this time: normal hearts contain microscopically visible fat; microscopically visible fat alone does not stamp a heart as demonstrating fatty degeneration; that fatty degeneration of the heart is much less common than supposed; that, clinically, fatty degeneration of the heart is therefore a very uncertain diagnosis.

SUMMARY

1. The clinical diagnosis of fatty degeneration of the heart is still made too commonly. It is a very uncertain diagnosis.
2. There are no symptoms peculiar to this condition, nor is there any pathognomonic sign for its diagnosis.
3. The diagnosis should be made by inference only. The etiological factors in fatty degeneration will help.

4. In reference to degenerative changes in the heart muscle, fatty and fibrous changes should not be differentiated clinically. This is Sir James Mackenzie's²⁰ view.

5. Fatty degeneration of the heart is a finding too frequently made post-mortem. The presence of microscopically visible fat in the muscle cell is not sufficient for this diagnosis.

6. In human cardiac muscle microscopically visible fat is normally present; it is by no means necessarily pathological. The fat resides in the sarcoplasm between the muscle fibrils and is arranged in longitudinal and transverse rows. Apparently the amount has no relation to the state of nutrition at the time of death; neither has the age of the individual (eight to fifty-six years), the color, nor the sex.

7. The picture presented by the diffuse red droplets (Scharlach R) or the black granules (osmic acid) closely resembles the classical illustrations that many of the textbooks of pathology utilize to picture fatty degeneration of the heart. True fatty degeneration, *e.g.*, the "tiger-heart," is recognized by the greater number and size of the granules, the evidences of inflammation, *e.g.*, nuclear changes, disappearance of striations, etc.

8. In all experimental work in which sections of cardiac tissue are stained for fat, normal conditions should be kept in mind and control performed whenever possible. In the investigation of twelve pathological hearts we found not one organ demonstrating fatty degeneration. Another writer performing work similar to ours reported "marked fatty degeneration" in every case.

9. The so-called pigment of brown atrophy of the heart, which is supposed to be an indication of degenerative processes, *e.g.*, senility, was found in moderate amounts in two healthy boys, one eight years old, the other fifteen.

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Discussion:

DR. ROHDENBURG: I think that Dr. Master is to be congratulated on his work. I can bear out one thing he speaks of. I have observed the localized fatty degenerations in a goodly number of cases associated with bundle branch lesions, where there had been a degeneration of the muscle fiber with large drops of fat and replacement fibrosis at the edge of the area of fatty degeneration.

DR. MACNEAL: I should like to ask if Dr. Master feels that the diagnosis of fatty degeneration should be made post-mortem in any case in which there is merely the presence of fat in the cells, or whether one should also have the fibrous replacement to justify such diagnosis at the present time.

DR. MASTER: In my work I only studied the ordinary cardiac muscle, and not the specialized tissue. In regard to the question of Dr. MacNeal, that is one of the points I am making, that you cannot diagnose fatty degeneration by the mere presence of fat in the cells. You must have all the other signs to do it.

CARCINOMA OF THE APPENDIX

ROBERT C. SCHLEUSSNER, M.D.

(From the Pathological Laboratory, Misericordia Hospital, New York City)

Since it has become customary to examine histologically all appendices removed at operation, carcinomas of the appendix have been frequently reported. It is estimated that 0.5 per cent. of all appendices removed are carcinomatous.

The specimen that I am presenting is therefore interesting only because it raises the question of the actual malignancy of the tumor. Batzdorf collected 186 cases and found that 6 per cent. were characterized by recurrences or metastases. But in this compilation are grouped both the common spheroidal celled carcinoma and the rarer true adenocarcinoma. Rolleston drew attention to the fact that these are two distinct groups and later writers on the whole confirm his view. The evidence that the typical adenocarcinomas are highly malignant seems quite conclusive (see Neugebauer; Voeckler). The malignancy of the common spheroidal celled carcinoma is still a matter of debate, only one case having been reported as definitely malignant (Lejars). Some writers indeed consider these tumors to be endotheliomas and do not believe that they are ever malignant (Neugebauer).

Using McWilliams' and Rolleston's compilation of cases I looked up the original articles in those cases where the tumor (including adenocarcinoma and spheroidal celled carcinoma) exhibited malignancy either clinically or histologically. McWilliams found three cases (reported by Baldauf, Hartman, Lejars) and Rolleston four cases (reported by Beger, Ruyter, A. O. Kelly, Elting). I have abstracted the various case reports below.

CASE I. Baldauf. Patient was a male, aged 38, operated upon under the diagnosis of acute appendicitis. An appendectomy was done. Examination of the specimen revealed a portion of the appendix wall infiltrated by nests of oval or polygonal cells with considerable light cytoplasm and vesicular nuclei. The growth extended into the appendix mesentery. I believe that this fairly may be considered as a carcinoma of the spheroidal celled type. The patient made an uneventful recovery and there is no further note as to

subsequent history. The only evidence indicating malignancy in this case is the invasion of the mesoappendix.

CASE 2. Hartman. Patient was a woman, aged 29, operated on under the diagnosis of acute appendicitis. At operation several nodules were felt in the mesoappendix. A portion of the cecum at its junction with the appendix was removed along with the appendix. The patient made an uneventful recovery and was seen again after four years. At this time she was well and no masses were palpable in the right iliac fossa. Examination of the specimen removed at operation showed a nodule involving the base of the appendix and also a similar one distal to it. The mesoappendix also showed two nodules. Section showed all of these nodules to be carcinomatous infiltrations of the tissue involved. The wall of the cecum was also found to be infiltrated by the growth. The tumor was classified as an atypical adenocarcinoma. This patient then with a histologically malignant (*i.e.*, invasive) growth was well four years after operation.

CASE 3. Lejars. Patient was a male, aged 27. He was operated upon under the diagnosis of chronic appendicitis and an appendectomy was done. No gross tumor was found at operation but it was noted that the appendix was as large as a middle finger and that it had a peculiar pale whitish color. The mesoappendix and cecum were normal and no enlarged glands were felt. The wound healed but in two and a half months the patient returned with a marked cachexia, a large mass in the right iliac fossa and flank, ascites, enlarged left supraclavicular glands and a subcutaneous tumor in the abdominal wall just to the left of the umbilicus. A laparotomy was done and a large mass was found involving the cecum and ascending colon and extending into the mesentery. A portion of the subcutaneous tumor to the left of the umbilicus was removed.

The appendix showed an epithelioma consisting of polygonal cells arranged in trabeculae and involving all layers of the appendix. Apparently the mesoappendix was not involved. The subcutaneous nodule removed at the second operation showed a histological picture identical with that found in the appendix.

CASE 4. Beger. Patient was a male, aged 47, who exhibited an ulcerating mass involving the skin in the right iliac fossa. At operation the mass was found to extend down to and involve the appendix, but also the cecum at the ceco-appendicular junction. Histologically it was a typical adenocarcinoma with cylindrical and goblet cells lining the lumina of the tubules. The evident involvement of the cecum at the time of operation casts doubt upon the primary origin of the tumor. The patient died a few hours after operation. At autopsy the retroperitoneal glands were found to contain metastases.

CASE 5. Ruyter. The patient was operated upon for appendicitis. Several years later he was readmitted to the hospital with a leg infection and a pyemia from which he died. At autopsy a small cystic tumor of the appendix stump was found. This turned out to be a colloid carcinoma on microscopic examination. There is no report of any examination of the appendix at the time of its removal. The author mentions this case among several carcinomas

of various types which had appeared in inflammatory tissue. There is nothing to prove that this tumor was a recurrent one.

CASE 6. A. O. Kelly. Case 4 cited by this author was a male, aged 63, who was operated upon because of recurring attacks of pain in the right iliac fossa. At operation it was noted that the appendix and intestines were studded with numerous grayish-white nodules like tubercles. An appendectomy was done. Examination of the appendix showed the wall replaced throughout by nests of epithelial cells varying much in size and shape. While solid alveoli of cells seemed to predominate, some hollow cylindrical arrangements lined by a single layer of epithelial cells were to be found. The presence of goblet cells is not mentioned. The mesoappendix was involved by the tumor. This patient died of shock one week after the primary operation as a result of secondary suture of the wound which had broken down.

CASE 7. Elting. This case was one in which appendix, cecum, ascending and transverse colon, and ileum were involved in a colloid carcinoma which seemed to have started in the appendix. Again, here, its origin must remain doubtful because of the extensive involvement when the tumor was first discovered.

Of these seven cases only four (Baldauf's, Hartman's, Lejars', and Kelly's) seem to be certain primary carcinomas of the appendix. The descriptions of the histological pictures presented in these various cases do not allow one definitely to group these cases together, but on the whole they would seem to belong to the group of spheroidal celled carcinomas. Granting that they belong to this group, which is the group to which the great majority of appendix carcinomas belong, it will be seen that there is definite clinical indication of malignancy in but one case (Lejars'). The other three cases present some evidence of malignancy in that the tumor is histologically invasive, but the clinical evidence of malignancy (metastases or recurrence) is lacking.

Though Lejars' case has been carefully studied and reported, its great malignancy in contrast to the other cases reported stands out so prominently that one thinks of a possible error of observation.

The case that I have to report is that of a woman aged 41 who was operated upon March 3, 1922, by Dr. Marton at the Misericordia Hospital.

Family and past history were negative.

Present illness: She always enjoyed good health until last summer (six or eight months ago) when she began to complain of backache. Three weeks ago she was seized with severe abdominal pain. Pulse and temperature were normal at this time. She vomited but once a few days prior to operation.

Operation: On examining the patient under ether it was found that Douglas' cul-de-sac was tense and a posterior colpotomy was done because of the belief that a pelvic abscess was present. No pus was found and a laparotomy was then undertaken. An appendix abscess was found. The appendix was but lightly adherent to the adjoining viscera and was easily removed. The pelvic viscera were normal and no evident mesenteric or retroperitoneal glandular enlargements were noted.

The patient had a stormy recovery. At first she did poorly but now (three months post-operative) she is steadily improving.

Pathological report: Gross examination of the specimen reveals an appendix measuring 6 cm. in length. Its proximal half measures 8 or 9 mm. in diameter, while the distal half measures about 12 mm. in diameter. The serosa is congested and shows slight roughening in small areas. Section through the wall at the proximal portion reveals the lumen filled in by a firm white tissue appearing in the gross like connective tissue. Section through

the distal half of the appendix reveals a different picture. Here the lumen is filled in by a uniform grayish-yellow tissue quite different from anything found in the usual appendix. Moreover the adjoining portions of the meso-appendix are closely studded by nodules of a similar appearance.

Microscopic examination: Sections taken through the distal half of the appendix reveal the central yellowish tissue to consist of large alveoli of epithelial cells. The individual cell is of moderate size, polygonal, shows a pale slightly eosinophilic cytoplasm and a large round nucleus, moderately rich in chromatin. Occasional mitotic figures are encountered. The serosa, muscularis and submucosa are all extensively infiltrated by similar alveoli of cells and the mesoappendix shows a similar invasion. The cell nests seem in some places to occupy lymph sinuses, but in other places they lie outside of these channels. The epithelial cells are sharply set off from the surrounding tissue. There is no suggestion of gland formation and no goblet cells are seen. The central cells of some of the alveoli show necrosis. Nowhere can blood

Photomicrograph showing invasion of mesentery with tumor cells growing in lymph sinuses. $\times 400$. (Made by Crocker Research Laboratory.)

vessels containing tumor emboli be seen. The connective tissue between the alveoli shows a moderate cellular infiltration consisting mostly of lymphocytes though polymorphonuclear leucocytes and plasma cells are also to be found. Here and there isolated tumor cells are to be found.

Sections taken through the base of the appendix show complete absence of tumor invasion either of the appendix itself or of the adjoining mesoappendix. The serosa is edematous and congested and shows a slight fibrosis. It exhibits a profuse cellular infiltration consisting of lymphocytes and polymorphonuclear leucocytes in about equal numbers. The mucosa has disappeared and the lumen is filled in by young connective tissue showing, especially toward the center, a profuse lymphocytic infiltration. A few neutrophile and eosinophile leucocytes are present. The small blood vessels throughout the section show accumulations of polymorphonuclear leucocytes.

Diagnosis: Subacute inflammation of an appendix exhibiting a spheroidal celled carcinoma with involvement of the mesoappendix.

SUMMARY

1. This paper is based on the premise that spheroidal celled carcinoma and adenocarcinoma of the appendix are different entities from a histopathological standpoint.

2. The malignancy of the adenocarcinoma is admitted.

3. Attention is called to the fact that but one case of the numerous spheroidal celled carcinoma reported has exhibited clinical malignancy, and the need of further reports to confirm the potential malignancy of this tumor is pointed out.

4. A spheroidal celled carcinoma of the appendix with involvement of the mesentery is reported.

In concluding, I wish to thank Dr. Marton for his courtesy in furnishing me with the clinical details of this case.

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The articles of Kudo and McWilliams have extensive references appended to them.

Discussion:

DR. VANCE: I have been very much interested in the question of carcinoma of the appendix. This type of carcinoma is very similar to a group of tumors which was described some years ago before this Society; they were tumors of the small intestine which had exactly the same histological appearance as this, and to a great extent the same type of growth—a very slight infiltrative growth into the lymphatic vessels. It is interesting to note the report of the infrequent malignancy. A few months ago I had occasion to find a tumor of the intestine in a man forty-eight years old who was killed by a fracture of the skull, and this tumor histologically was of the same type as the carcinoma of the appendix, but it had metastasized to the liver and lymph nodes. To judge by the pathological condition of the body, the tumor had had no effect on the health of the patient. Death was entirely due to the accident, but it is very interesting that the tumor had the same arrangement in trabeculae and cubical cells as in the carcinoma of the appendix.

DR. MEEKER: I wish to state that two months ago at the New York Post-Graduate Laboratory we had a series of nine appendices showing primary tumors of the type reported tonight by Dr. Schleussner, and of these only one had extended into the mesentery. They occurred between November 8th and January 20th, and the total number of appendices received during that time was 200, making the percentage of these tumors 4.5 per cent. for that period.

FINAL REPORT

Since the above article was written the case reported has come to a fatal termination in a manner which leaves little doubt that the tumor in question recurred and metastasized, even though no autopsy could be obtained. Dr. Marton, who observed the case from beginning to termination, has been kind enough to furnish the following data:

Patient was discharged April 11, 1922, after a stormy convalescence. Thereafter she gained weight; her appetite improved and she lost the cachectic appearance she had had just after operation. On June 14th she began to bleed freely from the vagina. Examination at this time showed the bleeding to

come from a broken-down area in the posterior vaginal fornix at the site where a drain had been placed into the cul-de-sac at the time of operation. Patient continued to bleed intermittently from this area for six weeks and during this time nodular masses appeared throughout her abdomen. These increased rapidly in size and the patient became increasingly cachectic. She died August 17, 1922.

The rapid course of the disease (clinical recurrence in three and one half months and death in five and one half months) corresponds with the course of the fatal case reported by Lejars.

The report of Lejars regarding the potential malignancy of the spheroidal-celled carcinoma of the appendix has herewith received its first corroboration in the literature in the sense that here again a case is reported that has exhibited a high degree of clinical malignancy.

THREE RAPIDLY FATAL CASES OF TRICHINOSIS WITH AUTOPSY REPORTS

*(Dr. Benjamin Morgan Vance, Assistant Medical Examiner
and*

Dr. Morton Ryder, Assistant Pathologist, Bellevue Hospital, New York)

The following report is a brief summary of three fatal cases of trichinosis, all occurring in the same family.

The probable source of infection was a meal of pork chops, eaten on November 11, 1921. At various intervals thereafter seven members of the family became ill, of whom three died in Broad Street Hospital. They were Margaret G., age eleven years, who died on November 28, 1921, about sixteen days after the probable date of infection; Mary G., age forty-nine years, date of death December 4, 1921, duration of disease about twenty-two days; and Joseph G., age eight years, date of death December 5, 1921, duration of disease twenty-three days.

The clinical histories of these cases will be described fully in another place. It is sufficient here to point out merely the rapidly fatal course of the illness. The fatal cases were autopsied by the Medical Examiner's Office, all within thirty hours after death.

Margaret, aged eleven, poorly developed and nourished, had œdema of the subcutaneous tissue in the lumbar region, and the legs appeared slightly puffy. Aside from injection of the meninges of the brain and spinal cord and the vessels of the brain itself, the viscera were practically normal.

Mary, aged forty-nine, slightly obese, presented negative findings except for the brain. The vessels of the dura, pia and brain were markedly injected. In the right frontal lobe were pinhead-sized hemorrhages, grouped in an area measuring several centimeters in diameter in the white matter, and scattered in the gray matter.

Joseph, aged eight, was considerably emaciated and the skin and mucous membranes were pale. There was a large abscess in and under the left pectoral muscle. The lungs showed early peribronchial infiltration. The right middle ear contained pus. There was a moderate excess of cerebrospinal fluid, which appeared rather turbid, and the blood vessels of the meninges of the brain were markedly injected. *Streptococcus hemolyticus* was cultured from the spleen. These pathological findings were interpreted as manifestations of streptococcus sepsis, the focus being the abscess in the left pectoral muscle.

None of the cases showed intestinal lesions nor any abnormal character of the intestinal contents.

Microscopic examination of these three cases showed practically identical lesions with a few minor differences. There was marked myositis in all the skeletal muscles examined, consisting of local infiltration of many polynuclear eosinophile leucocytes, lymphocytes, a few neutrophile leucocytes, and other inflammatory cells; in most cases these cells were grouped around the smaller blood vessels and between the muscle bundles.

Trichinæ were found in the muscle fibres in all three cases. The individual fibre involved showed atrophy and, in advanced cases, the formation of characteristic large cubical cells surrounding the worm, considered by many to be myogenic in origin and inflammatory in nature.

The grade of the process and the stage of development of the worm varied in different cases. In the little girl who died about two weeks after infection, some of the worms were forty times as long, others twenty times as long, as the red blood cell. Similar worms were present in the boy, who died after an illness of three weeks' duration, and they were especially evident in the abscess of the left pectoral muscle. Only one worm was found in the diaphragm of the woman, who lived about three weeks after infection. This embryo was about twelve times as long as a red blood cell, and was obviously a very early stage in the development of the worm. In all the muscles the trichinæ were extended, straight, or only slightly curved; none were coiled in a spiral or encapsulated.

The heart muscle showed some myositis, rather marked in the case of the little girl, where the areas of cellular infiltration involved much of the myocardium proper. In the woman and boy, however, there was only a mild grade of the process, confined to the heart muscle near the pericardial surface. No trichinæ were found in the heart muscle.

Sections of the brain and cord of the girl were negative. There was a

perivascular lymphocytic infiltration around some of the arteries in the brain substance, in the case of the boy. The woman, however, showed marked meningitis and hemorrhagic encephalitis. The vessels of the cerebral cortex were plugged by fibrinous thrombi and the sub-arachnoid space was infiltrated by large epithelioid and other inflammatory cells. The area of encephalitis showed marked perivascular hemorrhage, but scarcely any cellular response. There were plugs of ovoid outline in some of the finer blood vessels in this region, but it was impossible to identify them as parts of the trichina embryo. However, it is reasonable to conclude that the trichinosis was responsible in some way for the meningitis and encephalitis. The intestine of the boy was sectioned, but nothing abnormal was found.

The other viscera showed nothing of significance.

The interesting features of these three cases are, first, the rapid and fatal course of the disease, reckoning from the probable date of infection; second, the different sizes and stages of development of the intramuscular trichina embryos. According to Staubli, postmortem examinations on cases that have a clinical course of less than three weeks are almost unknown or, at least, quite rare. The girl died in slightly over two weeks' time, while the woman and boy succumbed a week later. The fact that two of the deceased were children appears to be a rather unusual feature, as the disease is supposed to run a much milder course in children than in adults.

The differences in size and the general lack of coiling of the various intramuscular embryos indicate a recent infection and also a discharge of trichina embryos into the intestinal lymphatic circulation in successive intervals. This is quite in keeping with the life history of the adult trichina forms, as it has been observed in the intestinal tract.

The meningeal and brain lesions in the case of the woman are extraordinary, but have been described before by Frothingham and others. The muscular lesions, however, are typical of the disease, though the process is, perhaps, a little more acute than is ordinarily seen in sections of skeletal muscles removed at biopsy and autopsy.

Discussion:

DR. MACNEAL: I should like to ask if you had a large amount of muscle tissue preserved from each case. I understand this was an accidental finding made when the tissues were examined microscopically.

DR. VANCE: We saved as many muscles as we could.

DR. MACNEAL: Did you save any of the extra-ocular muscles?

DR. VANCE: No, we only saved those of the neck, of the larynx, and of the diaphragm.

A CASE OF ACUTE LYMPHATIC LEUKEMIA

(From the Laboratories of the Lenox Hill Hospital, New York City)

A. L. GARBAT, M.D., AND G. L. ROHDENBURG, M.D.

The present case is presented not because the condition described is novel but because the opportunity was offered of a thorough observation and of applying all of the usual methods of treatment.

The patient, a young girl aged eighteen, had an uneventful past and family history. Five weeks before the onset of the disease which caused her death, she was immunized in the usual fashion against typhoid fever, the vaccine used being a sensitized preparation. At the conclusion of this immunization she went to a girls' camp for the summer. After being in camp about ten days ecchymoses appeared on the face and extremities and menstruation, which was then present, became very profuse and continuous. At the same time a temperature was present. She came under our observation five days after the onset of these symptoms.

Her parents had noted that in the previous spring she had been rather pale and had tired more easily than before. Physical examination showed an exceptionally well-developed muscular girl, whose general appearance indicated an acute anemia. The only positive physical findings were: a spleen enlarged so as to reach almost the median line of the abdomen, palpable glands in the axillæ and neck, and a metorrhagia of profuse character. The results of laboratory investigations were negative except for the changes in the blood presented in the accompanying table.

The bleeding from the uterus keeping up and the clinical diagnosis of an acute lymphatic leukemia being made, a transfusion was done on the tenth day and again on the twelfth day of the illness. Between the two transfusions radium was applied to both ovaries. The total white count had commenced to fall before the first transfusion and on the thirteenth day of the disease was 400 as compared with 44,000 on the second day of the disease. On the seventeenth day a third transfusion was given and in the interval between the second and third transfusion two injections of 0.1 gm. of silver-arsphenamine were given. During this period the uterine bleeding had diminished considerably but had not stopped. In order to completely control the bleeding the uterus was treated with a copper electrode and the galvanic current. The leukopenia continued, though the differential count showed a gradual recession of the lymphocytes. The hemoglobin and red cells gradually increased and

TABLE

| Day of Disease | Total Leucocytes | Lymphocytes | | Hemoglobin | Red Blood Cells | Remarks |
|----------------|------------------|-------------|-------|------------|-----------------|---------------------------------------|
| | | Small | Large | | | |
| 2..... | 44,000 | 73 | | 65 | 3,560,000 | Platelets 250,000 |
| 5..... | 5,400 | 49 | 40 | 76 | 3,400,000 | |
| 6..... | 20,700 | 84 | 12 | 72 | 3,200,000 | |
| 7..... | 23,000 | 88 | 8 | 60 | 2,600,000 | |
| 8..... | 9,800 | 98 | | 50 | 1,800,000 | |
| 9..... | | ... | | ... | | Transfusion, 540 c.c. |
| 10..... | 400 | 100 | | 36 | 2,230,000 | Radium, 100 mg., 12 hours, to ovaries |
| 11..... | | ... | | ... | | Transfusion, 800 c.c. |
| 12..... | 400 | 79 | 21 | 49 | 1,900,000 | Silver salvarsan, 0.1 gm. |
| 13..... | 1,000 | 88 | 12 | 47 | 2,100,000 | |
| 14..... | 400 | 80 | 20 | 38 | 1,500,000 | Silver salvarsan, 0.1 gm. |
| 15..... | 700 | 98 | | 38 | 1,650,000 | |
| 16..... | | ... | | ... | | Transfusion, 800 c.c. |
| 17..... | 700 | 98 | | 49 | 2,144,000 | Silver salvarsan, 0.1 gm. |
| 18..... | 1,000 | 70 | | 51 | 2,384,000 | |
| 19..... | 1,200 | 68 | | 48 | 2,380,000 | Silver salvarsan, 0.1 gm. |
| 20..... | 800 | 70 | | 48 | 2,496,000 | |
| 21..... | 700 | 68 | | 42 | 1,840,000 | Radium, 100 mg., 12 hours, to spleen |
| 22..... | 800 | 72 | | 45 | 1,980,000 | |
| 23..... | | ... | | ... | | Transfusion, 320 c.c. |
| 24..... | 800 | 44 | | 50 | 2,128,000 | Silver salvarsan, 0.1 gm. |
| 25..... | 800 | 23 | | 50 | 2,248,000 | |
| 26..... | 1,500 | 33 | | 60 | 2,544,000 | Nucleated red cells |
| 27..... | 1,400 | 44 | | 55 | 2,460,000 | |
| 28..... | 1,800 | 42 | | 55 | 2,400,000 | Nucleated red cells |
| 29..... | 2,000 | 32 | | 53 | 2,722,000 | |
| 30..... | 2,000 | 23 | | 45 | 1,820,000 | Transfusion, 530 c.c. |
| 31..... | 2,700 | 24 | | 45 | 1,960,000 | |
| 32..... | 2,600 | 24 | | 48 | 2,230,000 | Transfusion, 530 c.c. |
| 33..... | 3,200 | 16 | | 40 | 1,800,000 | |
| 34..... | 3,200 | 26 | | 43 | 2,240,000 | Transfusion, 530 c.c. |
| 35..... | | ... | | ... | | |
| 36..... | 4,600 | 15 | | 54 | 2,880,000 | Transfusion, 530 c.c. |
| 37..... | 3,800 | 14 | | 52 | 2,700,000 | |
| 39..... | 4,800 | 20 | | 64 | 2,240,000 | Transfusion, 530 c.c. |
| 41..... | 6,000 | 20 | | 72 | 2,800,000 | |
| 43..... | 12,000 | 24 | | 81 | 3,700,000 | Transfusion, 530 c.c. |
| 46..... | 9,800 | 17 | | 89 | 4,200,000 | |
| 50..... | 99,600 | 38 | | 102 | 4,330,000 | Transfusion, 530 c.c. |
| 51..... | 124,000 | 50 | | 95 | 4,224,000 | |
| 52..... | 97,000 | 55 | | 96 | 4,340,000 | Transfusion, 530 c.c. |
| 53..... | 80,600 | 56 | | 100 | 4,460,000 | |
| 54..... | 72,400 | 64 | | 96 | 4,320,000 | Transfusion, 530 c.c. |
| 55..... | 182,400 | 86 | | 80 | 4,768,000 | |

the temperature still continued. A fourth transfusion was given on the twenty-fourth day and a fifth on the thirty-eighth day of the disease, injections of silver arsphenamine and radium applications being continued between the transfusions as indicated in the table. During this period the temperature receded, the total white count gradually rose to 3,200; the differential count approached the normal, while the red cells and hemoglobin remained about the same. The spleen in the meantime returned to its normal size, the glands were no longer palpable and for several days there was a normal temperature.

It was thought at first that we were dealing not with a true leukemia, but with one of those leukemic-like reactions which others, notably Cabot, have described and which we have twice encountered, once during a pneumonia and again in the course of an intestinal infection of unknown etiology. Unfortunately however five days before death the picture quite suddenly changed; the total white count rapidly rose to 182,000 and the differential count again assumed the characteristics of leukemia, though the hemoglobin and red cells remained high. Two days before death a few ecchymoses appeared on the cheek, and the post-auricular and axillary glands again became enlarged. The spleen remained small until the day before death when it increased in size from hour to hour with almost unbelievable rapidity, changing in less than fourteen hours from a nonpalpable size until the edge was palpable across the median line. Death occurred with a cardiac collapse.

The case is presented as one of acute leukemia during which there occurred a phase of leukopenia followed by an almost complete return to the normal and then a recrudescence of the leukemic phase. Though the initial impression was one of therapeutic success, the final outcome conclusively showed the erroneous nature of this impression.

Discussion:

DR. ROSENTHAL: I would like to inquire was it the radium that did all this. We know that radium is detrimental to the bone marrow and blood cells, and it is a question whether the marked destruction of the bone marrow produced the marked diminution of the cells at first, and later on there was a sudden increase and outpouring of the cells which were previously inhibited.

DR. DARLINGTON: At the fiftieth day had the physical condition improved?

DR. ROHDENBURG: The decline in the leucocyte count had occurred before radium was applied and before the first transfusion had been given. On the morning of the day the radium was applied the leucocytes were around 1,000; they ran between 400, 800, and 1,500 for nearly two weeks. The decrease in cells I do not think can be attributed to the radium.

On the fiftieth day the physical condition was such that all preparations were made to take her to the country. Her father had gone to one of the Jersey coast resorts, and while he was gone she developed a few ecchymotic

spots on her cheek. The spleen had enlarged for the second time until eighteen hours before death, when it increased in size from hour to hour. This sudden increase in size caused excruciating pain.

MULTIPLE THROMBOSIS WITH POLYPOID THROMBUS IN THE RIGHT HEART

W. A. CHIPMAN, M.D.

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Cardiac thrombi, exclusive of the vegetation of acute valvulitis, are of two types, namely, globular and polypoid thrombi. Globular thrombi are much the more common of these two types. They vary in size from that of a pea to that of a hen's egg. They present a number of characteristics, such as multiplicity, with adjacent thrombi often connected by a fine meshwork, broad or sessile attachments, bland softening of the central portion with the peripheral portion remaining as a thin shell which rarely bursts, and degeneration of the underlying myocardium. This type of thrombus rarely undergoes organization.

Cardiac polypoid thrombi are a relatively rare pathologic entity. In Welch's series of 33 authentic cases, 25 sprang from the wall of the left auricle, usually the septum, 4 from the left ventricle, and 4 from the right auricle. From the time his paper was published (1899) to the present writing, no additional cases are listed in either the Quarterly Cumulative Index or Index Medicus, unless certain of the cases reported as myxomata are in reality organized thrombi.

Cardiac polypoid thrombi present a number of noticeable features. There is no discernible cause for their occurrence in many instances, the hearts containing them being normal except for changes secondary to the thrombus. They are solitary formations rarely occurring with other thrombi. From the above statistics, it is seen that most of these thrombi occur in the left auricle. They are usually attached at the fossa ovalis by a short pedicle and simulate true cardiac tumors, being firm or gelatinous,

ovoid in shape, usually with a smooth glistening surface, not unlike endocardium. These growths may show calcified, pigmented or atheromatous patches. The color varies from a yellowish fat-like substance to brownish red. Differing from all other cardiac thrombi, these polypoid growths are usually organized, the process often being so advanced as to simulate a myxoma or fibroma. In those less organized, the thrombus consists of red cells, granular detritus, leucocytes, pigment, fibrin and occasional connective tissue cells, together with newly formed blood vessels.

Three theories have been advanced to account for the origin of these polypoid thrombi, namely, thrombosed varices (Bostroem), hemorrhage into the septal wall (Bostroem), and degeneration of the myocardium (Krumm). Bostroem cites four cases: two representing thrombosed varices, the third that of a ball thrombus which had recently broken from its septal attachment and was histologically a thrombosed varix, and the fourth that of a polypoid thrombus with hemorrhage into the septal wall as the etiological factor. On the other hand, Krumm cites one case in which there was localized disease of the heart wall.

There is considerable dissension, especially among the German writers, as to whether "tumors" arising for the most part from the fossa ovalis of the septum of the left auricle should be classed as polypoid thrombi or as myxomata, or whether both exist. The type of tumor classified as a myxoma is gelatinous, yellowish to brownish red, polypoid or oval in shape, sessile, with a narrow or broad pedicle, and has a glistening smooth surface, not unlike endocardium. Histologically, they have a matrix much like Wharton's jelly, give a positive mucin reaction (mucicarmin "Mayer," mucihematin "Mayer," or thionin "Hoyer") and have newly formed blood vessels. Thorel considers most of these to be organized thrombi, whereas Ribbert maintains they are true tumors.

The case to be reported presented the following history:

The patient, a white man 60 years of age, was admitted to the service of Dr. Theodore Abbott, Bellevue Hospital, on April 10, 1922, and died six days later. On admission, he complained of dyspnoea and edema of the eyelids and feet. In addition to the dyspnoea and edema, which had been present to a

minor degree for six or seven years, he complained of cough, with blood-streaked sputum, for two months prior to admission.

Physical Examination. Physical examination showed puffiness about both eyes, unequal pupils which failed to react to light but reacted sluggishly to accommodation, moderate albuminuric retinitis, and chronic conjunctivitis. There were abnormal venous pulsations in the neck. The heart was enlarged,

fibrillating, with a pulse deficit of about sixteen beats to the minute, with a double murmur at the base transmitted down the left side of the sternum, and a systolic murmur at the apex. There were signs of pneumonia in the right

upper chest. The liver was palpable, but neither pulsating nor tender. There was questionable ascites, with edema of the lower extremities, extending to the knees.

Urinalysis showed albumin in rather large amounts, a specific gravity of 1.020, hyaline and granular casts and blood cells. The phenolsulphonephthalein test was 25 per cent. in the first hour, and 30 per cent. in the second hour, and the blood chemistry showed a non-protein nitrogen of 38.5 mg. and a creatinine of 1.3 mg. per 100 c.c. of blood. The blood pressure was 150 systolic, 85 diastolic.

Necropsy Findings: Inspection of the body revealed edema, otherwise nothing of note. On opening the abdomen, there were about 200 c.c. of fluid in the peritoneal cavity. There likewise appeared to be fluid in both pleural sacs and in the pericardial sac (chest opened via diaphragm). The heart was large with a dilated right auricle. On opening the right auricle, there was a polypoid mass, 45 cm. in length by 3 cm. in diameter, attached by a short pedicle 1 cm. in diameter to the auricular septum at the fossa ovalis, and hanging down to partially occlude the tricuspid valve. It was soft, semi-fluctuant, yellowish, except at the base where it was brownish red. The surface was smooth, glistening and appeared to be covered by endocardium. In the auricular appendage there were several gray thrombi, measuring from 0.5 to 1.5 cm. in diameter. The tricuspid valve appeared normal. At the apex of the right ventricle, among the columnæ carneæ, was a gray thrombus, 1 cm. in length and half as wide. The mitral leaflets were thickened, but the opening admitted two fingers. The cusps of the aortic valve were fused for about 3 mm. The aorta, especially the arch, was roughened, somewhat wrinkled, thickened, but not calcified. The coronary arteries were somewhat sclerotic.

The upper and middle lobes of the right lung showed lobar pneumonia. There was a stellate "scar" of the pleura over the lower lobe of the left lung. The liver was of the nutmeg variety. The kidneys were normal in size, but otherwise presented the picture of chronic arteriosclerotic nephritis. The head and neck were not examined.

Anatomical Diagnosis: Heart—Multiple thrombi—right auricle and right ventricle, aortic stenosis, sclerosis of aorta and coronary vessels, hypertrophy and dilatation. Lungs—Organizing lobar pneumonia (right upper and middle lobes and left lower lobe), fibrous pleuritis (right), "syphilitic" scar of pleura. Kidneys—Chronic diffuse nephritis (arteriosclerotic). Liver—Chronic passive congestion with central necrosis. Petechial hemorrhages on inner side of elbow joint, chest and legs.

Histologic Findings: The heart showed moderate hypertrophy in general, with some hyperchromatosis of the nuclei throughout. There was little increase in fibrous tissue, except in sections near thrombi. Microscopic sections through the septum and polypoid thrombus showed hyperchromatic muscle nuclei, with swollen sarcoplasm. The polypoid thrombus consisted of fibrin with little cellular structure except for great numbers of newly formed blood vessels, and clusters of endothelial cells in which a lumen had not been formed. There was some lymphocytic infiltration about these cell cords. In one pole of the polypoid thrombus there was a large area of fresh hemorrhage, con-

sisting of well-preserved red corpuscles, through which coursed many newly formed and forming vessels. Scattered throughout there were small areas of blood pigment (old hemorrhage). At the site where the thrombus was attached to the auricular wall there was marked focal thickening of the endocardium from which a spur passed inward, separating the muscle bundles. This plaque consisted of relatively acellular, edematous, fibrous connective tissue in which were numerous capillaries. Scattered through this area there were numbers of rounded or oval structures, with small hyperchromatic nuclei, and with purplish, granular cytoplasm (degenerated muscle cells). Along the inner border of this area there was marked round-cell infiltration, especially marked about some of the vessels. The endocardium at a corresponding point on the opposite side of the septum showed similar changes. In places, this plaque merged imperceptibly with the polypoid thrombus, whereas, in other places, the line of demarcation was quite distinct. The endothelium of the auricle appeared to reflect onto the pedicle, and continue over the mass.

Microscopic examination of the auricular muscle and thrombi in the appendage showed marked degeneration of the muscle with indistinctly staining sarcoplasm containing vacuoles. The nuclei were swollen, either very pale or deeply hyperchromatic. The endothelium beneath the thrombi was destroyed. All the thrombi presented a similar histologic picture—collections of detritus through which were indistinctly formed granular columns, and, about the periphery, leucocytes, red cells and fibrin. The thrombus in the ventricle presented the same picture, except for beginning organization along the ventricular border. The muscle beneath the ventricular thrombus showed one or two focal areas of fibrous connective tissue in which there was round-cell infiltration.

Microscopic examination of the upper lobe of the right lung showed organizing pneumonia. Sections through the pleural "scar" of the left lower lobe showed marked thickening of the pleura, extensive perivascular round-cell infiltration, and marked endarteritis.

Examination of the kidneys showed advanced nephritis of the arteriosclerotic variety. The liver histologically showed chronic passive congestion with central necrosis. The spleen also showed chronic passive congestion.

Discussion:

DR. BISHOP: There is apparently a case of cardiorenal disease with fibrillation and paralysis of the auricle. This subject is highly important at the present time, because in the last two years quinidin sulphate has come into use. This drug apparently has the power of restoring contraction to some of these auricles which have been paralyzed for a long time, and about five per cent. of these old cases of fibrillation in degenerated hearts of just the type described here have shown embolism after the contraction of the auricle has been restored, so the existence of these thrombi clinically must be fairly frequent in these old cases. This makes it of doubtful good judgment to treat very old cases of fibrillation with quinidin. The important matter would be to have some criterion by which we could judge whether these auricles were

so affected before we had a chance to examine them pathologically, because testing them out by the quinidin treatment is a rather dangerous way of proving that thromboses do exist.

DR. MACNEAL: Was quinidin used in this case?

DR. CHIPMAN: He received tincture of digitalis, ℥ xx, every four hours, but no quinidin. Before death he received adrenalin, ℥ xv, every fifteen minutes for six doses with no benefit.

OSSIFICATION OF ARTERIES

LEILA CHARLTON KNOX, M.D.

Ossification as a phase of late stages of chronic inflammation and subsequent to calcification is not in certain organs a particularly rare lesion. In the choroid coat of the eye, for instance, it is found to follow 89 per cent. of the infections which are severe enough to cause loss of the organ; and small osseous deposits have been found in the lungs by Pollak and Lubarsch in about 70 per cent. of those which were the seat of chronic pulmonary infections, generally tuberculous. Almost every organ has been found ossified to a limited extent but so irregular is the process that it may scarcely ever be anticipated. In animals the reverse is true, and inflammatory lesions in rabbits, dogs, and birds readily ossify following comparatively slight trauma or short-lived infection. Illustrative of this are the experiments of Harvey who initiated the production of bone in the adventitia of the aortas of a series of rabbits by a single application of silver nitrate to the outer surface of the vessel; and the earlier work of Sacerdotti and Frattin who found bone in the kidneys of rabbits three months after the ligation of the renal artery. These experiments however shed little light on the cause of the process in human beings, nor are we able to understand upon what the difference in incidence depends. It cannot be explained as directly due to the calcium content of the blood for the differences between animals, and between man and animals, are so slight that no importance can be attached to them, the whole blood of rabbits, according to Abderhalden, containing 0.072 parts of calcium per 1,000, of dogs 0.055, while that of man contains from 0.090 to

0.110, these figures varying only slightly and in a few conditions.

But this is of course only one factor in a complex reaction. It is certain that all bone formation except in osteogenic tissue is preceded by calcification and that the precipitated salts are an essential to the production of the osteoid matrix and conversion of the fibroblasts of granulation tissue into osteoblasts and to the production of the marrow cells. The initial step in this process, the deposition of calcium, may take place in any tissue or organ, epithelial, connective tissue or endothelial, and is rather common in neoplasms. It is not dependent upon the age of the subject as calcification of portions of the cardiac muscle has been observed by Jacobsthal in an infant three weeks of age, and calcified lymph nodes in children are by no means unusual. Once deposited it may be again absorbed for Schujeninoff who studied a series of laparotomy wounds in patients who died shortly after operation found that between the ninth and twenty-fourth day seventeen out of twenty-four contained calcified granular deposits. In rabbits similar deposits were formed in the same way, and later largely disappeared. This the writer thought to be a sequel to the colloidal degeneration of the muscle. It may undoubtedly follow many other forms of degeneration, but is especially frequent after hyaline or fatty changes as in the necrotic walls or centers of old abscesses. Considering the notable frequency of hyaline degeneration in tumors of the uterus, calcification is rather rare; and although Klotz and Mönckeberg have upheld the importance of fatty degeneration, it is interesting to observe that calcification in the liver is very rare indeed, while fatty lesions in this organ are a matter of daily observation. Klotz, who has urged the importance of preliminary fat necrosis and the intermediate formation of calcium soaps, also explains the finely granular arrangement of the calcium in the walls of the aorta as a result of the preliminary suspension of fatty globules in the perivascular lymph. He also believes that the frequency of calcification in striated muscle is due to the readiness with which it first undergoes fatty degeneration.

Wells has shown that the chemical composition of normal bone and of pathologic areas of calcification are the same, about

84 per cent. of each being composed of calcium phosphate. This observation gives rise to the question as to whether the preliminary step in the tissue to be calcified is the formation of some substance with a high affinity for calcium, possibly phosphoric acid derived from the degenerating nuclei of the part; and Croftan finds that deutero-albumose, formed during autolysis, has such an affinity.

Another important factor in the chemistry of the situation is the change in local reaction which would permit precipitation of the calcium. For this an increase in alkalinity or at least a diminished amount of carbon dioxide is necessary. Such a change of balance has been used as the chief explanation of the frequency of calcification in the walls of portions of the arterial system as compared to that of the veins where the carbon dioxide content of the blood is higher. This may also account for the phenomenon of "metastatic calcification" or precipitation of calcium from the blood when the content is higher than normal due to bone destruction by tumors, etc.

Wells thinks that a third factor may be the affinity of the under-nourished cells in the semi-devitalized tissue for the serum proteins with which the calcium is combined, thus freeing unusually large quantities of calcium. This author, however, believes, on experimental ground, that the deposition of calcium is dependent not upon the presence of any given chemical substances, but upon specific absorption affinities and physico-chemical relationships only incompletely understood.

Whatever they may be, they are much more regularly encountered than are those necessary to produce the osteoid and osseous tissues. The indispensable factor for this phase is generally recognized as increased vascularity with consequently actively growing fibroblasts in the region of the calcific plaques, this probably being due to irritation, perhaps largely mechanical, but possibly chemical. This is apparently a reparative process which closely approaches, without ever reaching, a neoplastic one, occurring as it does usually in senile tissues in which other proliferative changes are in abeyance and degenerative or atrophic ones predominate. There is general agreement that the process

is one of metaplasia, and that soon after the bony deposits are laid down there are formed foci of cells of varying types, lymphocytes, plasma cells, myelocytes and even erythroblasts are reported, with occasional multinucleated cells of the type normally seen in bone marrow. The source of these cells so rarely seen outside the marrow spaces has aroused much speculation, but Mönckeberg and others are of the opinion that they also are formed by direct metaplasia of the connective tissue elements and are not transported by the blood stream from the normal situations. The absorption of the calcium salts and the deposition of osteoid tissue and eventually fully formed Haversian canals and lacunæ follow just as in periosteal new bone.

In spite of the frequency of calcification in atheromatous blood vessels, ossification is by no means common. It is most often seen in the arteries of the lower extremities in cases of senile or diabetic gangrene, and it is doubtful whether it has ever been observed in a young person, even in those rare cases which have shown calcified and arteriosclerotic vessels. Except in the case of DeWitt in which the femoral vein contained a sheath of bone in the adventitia continuous with an extensive traumatic myositis ossificans, the lesion has not been described in veins. Marchand early mentioned the occurrence of bone in the crural artery and Mönckeberg first described the same lesion in an aorta. Orth stated that the process was less frequent in the aorta than in the other arteries, and its occurrence can in no way be dependent upon the erosion or stimulation of pre-existing cartilage or periosteum or else it might be expected to be more frequent here due to the relation of the aorta to the vertebral column. In the case of Hensen who found bone in the wall of an aneurysmal sac in apposition with the tracheal rings the perichondrium was regarded as the probable source of the bone cells.

The relation of cartilage to the new bone has been studied carefully, but as this tissue is much rarer than bone, except in neoplasms, it has only been found a few times. Rosenstein in 1900 first described both bone and cartilage in a calcified aortic valve, and Marburg in the following year observed minute cartilaginous areas in the intima of the cerebral arteries in three cases,

all of which showed advanced vascular degeneration. Mönckeberg later saw several instances of heterotopic cartilage in the media of the tibial arteries, and Buerger and Oppenheimer mention it as very frequently present. All authors are agreed that it does not necessarily precede the bone formation and has no part in it.

The literature as a whole contains reports of only thirty-five instances of ossification of the arteries: one in the carotid, eight in the aorta, seven in the heart valves, one in the axillary artery, and twenty-one in the extremities. Detailed summaries of these cases are found in the literature, perhaps the most complete being that of Bunting, published in 1906. The case of Poscharissky furnishes the only record of an ossified myocardium. An effort was made by this writer and by Kryloff and Mönckeberg to determine the relative frequency of the lesion by examination of a series of cases. Mönckeberg, who sectioned the arteries in 130 cases, found bone 10 times, or in 7.6 per cent. Poscharissky studied the vessels of 150 persons dying of arterial disease and obtained four positive results, or 2.6 per cent.; while Kryloff found ossification in five of thirty-two calcified arteries, or 15.6 per cent. From these figures it may, therefore, be expected in scarcely more than 6 per cent. of the cases of severe arterial degeneration, and is more than twice as frequent in the lower extremities as in the aorta or heart valves.

PERSONAL CASES

The vessels in the cases presented are sections of the anterior and posterior tibial arteries, one from a case of diabetic, and the other of senile gangrene. The patient in the former case was a man aged sixty-five, who had observed redness and swelling of the left foot for a year, and had suffered considerable pain for the latter six months. The blood sugar ranged from 110 to 152 mg. per 100 c.c. of blood, and the urine usually contained a faint trace of sugar, in spite of a very limited diet. Suppuration of the toes and tendon sheaths necessitated amputation in the middle of the calf. A few weeks after this operation it became necessary to remove one toe from the other foot because of the infection which was in progress here also. The middle phalanx of this toe was the seat of an active ossifying periostitis,—a fact which might suggest a tendency on the part of the individual to produce bone in different situations under the influence of certain stimuli.

The arteries of the amputated foot show intimal thickening as well as medial ossification. In most sections the bone extends throughout almost all the circumference and replaces the muscle coat. Its relation to the intima varies. In some sections it seems to bulge forward and encroach upon the

Posterior tibial artery showing ossification of media with endarteritis.

lumen, thus forming the ringed appearance described by Mönckeberg. Elsewhere a few muscle fibers cover the bone and in many of them a heavy layer of fibrous tissue replaces the intima. In other sections a delicate parietal thrombus is attached over about half of the circumference and occupies the greater part of the lumen. This is the usual type of an early organized thrombus containing secondary thin-walled vessels, infiltrating cells and pigment. The structure of the bone is very close to normal although Virchow stated that the cells of heterotopic bone were usually smaller. Osteoclasts are present, though infrequent, and osteoblasts are numerous.

The marrow, which is fairly abundant, is composed of a loose fibrous and fatty reticulum, containing large and very delicate fibroblasts, their nuclei larger than normal, possibly partially due to edema. Polynuclear neutro-

philes, mononuclears, probably plasma cells, phagocytic cells containing hemosiderin and numerous lymphocytes are found throughout. Erythroblasts cannot certainly be identified.

The second case was that of a man aged seventy-four. He suffered for one year from severe pain in both feet. The calves and feet were cold, edematous, and bluish in color, the skin dry, scaling and atrophic. The pulse on the right side was barely perceptible in the popliteal space. After a few weeks, infection and necrosis of the toes of the right foot necessitated amputation of the extremity at the knee.

Both anterior and posterior arteries showed an inflammatory reaction in all of the coats with much disorganization of them; also calcification of the media with ossification, the latter more extensive in the posterior branch. These vessels show some infiltration of the adventitia and a delicate lamina of bone in the outer portion of the media. The inner half is largely calcified, the elastic lamina is swollen, homogeneous and uniformly calcified, and there is an endarteritis which has produced much fibrous tissue and left only a minute lumen patent. The adjacent veins show a chronic endophlebitis. The marrow is well developed around the bone in the larger arteries, much of it being fatty, the rest cellular with myelocytes and normoblasts.

Both of these specimens, therefore, exhibit calcification of the media with the production of considerable quantities of bone accompanied by the usual lesions of arteriosclerosis. Mönckeberg believes that medial calcification is more common than arteriosclerosis, but may occur together with it or as an independent condition and that ossification may be secondary to either. Aschoff thinks it doubtful whether they are truly independent conditions, and points out that no especial etiology is known for either disease, nor can the etiology of the two be separated. Marchand believed that the type of degeneration depended somewhat upon the type of artery, medial calcification occurring in those vessels which were essentially muscular in type with well-developed medial coats; and intimal sclerosis in arteries of the elastic type as the aorta and larger vessels. Kaufmann adheres to this view. The importance of special toxins cannot be overlooked, since it is known that adrenalin may experimentally induce calcification or ossification, or both. But the tendency is strong in many branches of medicine and pathology to explain one uncertainty by means of another equally intangible one, and to assume the presence of an endogenous toxin which, while of great aid in such a discussion, must be under-

stood to possess no basis of demonstrated fact. Whatever undiscovered agency may contribute to the result it is unquestionably augmented by the peculiar exposure of the vessels of the lower extremities to trauma, cold, and the variations in circulatory conditions due to these factors and to gravity.

CONCLUSIONS

1. Ossification of the arteries probably occurs in about six per cent. of the vessels of the extremities which show severe arterial degeneration. It is more than twice as frequent in these vessels as in the aorta and cardiac valves.

2. Ossification of the arteries takes place usually in the medial coat, though occasionally in the intima also.

3. It follows medial calcification with or without endarteritis, but is most common where the two are combined. It is usually not associated with cartilage, but is the result of metaplasia of fibroblasts of the adjacent granulations as they impinge on the calcific plaques.

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WELLS: *Chemical Pathology*, 4th Ed., Philadelphia, 1920.

Discussion:

DR. MOSCHCOWITZ: Ossification of the arteries has been reported rather frequently. Oppenheimer and Harvey have reported it in recent years. From the analogy to pathological ossification which occurs in other parts of the body, it does not seem to me as if it were necessary to make a separate group for ossification in the arteries. It seems to me that ossification in the arteries follows the general laws for pathological ossification of other parts of the body. The sequence of events is this: death of tissue, which may be either necrosis or hyalinization, calcification, and ossification. Why certain tissues may ossify, while others will not, is a problem that I do not think anybody is able to answer at present. Certainly an exquisite adjustment of the blood supply is one of the necessary factors. More interesting I think than the mere presence or absence of ossification is the genesis. Some years ago I presented a series of five cases of ossification of the ovary. By good fortune these cases presented a continuous series of lesions illustrating the genesis of the ossification very beautifully. I could show that the ossification occurred in the process of angio-genesis—that it was in the process of formation of blood vessels that the ossification occurred; that developing blood vessels presented first on the surface of the ossification in little scalloped portions of the ossification, and that if you followed these developing blood vessels you could see a gradual senescence of the blood vessels, and of the cells which take part in the formation of the blood vessels. These cells are entirely derived from the mesoderm, and are eventually the progenitors of all the cells of the bone, so that not only do these blood vessels form the marrow, but the osteoblasts and bone cells, and the process is very similar to that which is seen in endochondral ossification.

DEMONSTRATION OF AN AUTOMATIC PIPETTING APPARATUS

LEON H. CORNWALL, M.D., AND G. P. SCHMITT

This apparatus was devised to facilitate pipetting. It consists of a glass section through which the liquid is aspirated and delivered and a metal section. The latter functions as the automatic operating portion.

The glass section is composed of a syringe, the distal end of which is continued as a capillary tube. A few centimeters from the distal end of the syringe there is a curved portion of capillary

tubing disposed at right angles to that portion which is a continuation of the syringe. In each arm of the capillary portions there is a bulbous dilatation with a ground joint and a conical

glass bead. These beads act as valves. When one is open the other is closed and *vice versa*.

The metal operating mechanism is essentially a syringe that is operated by forcing air into the barrel. By means of a very simple adjustment the excursion of the metal piston may be regulated for the aspiration of the desired quantity of liquid. The metal piston descends by gravity when the pressure of air is released.

By means of a connecting arm of metal both metal and glass pistons move together. The apparatus may be attached to a ring stand or clamped to the neck of a bottle or flask.

We have used it for Wassermann serology and colloidal gold work at the City Hospital for several months and I can assure you that it saves about 50 per cent. of time in pipetting. Whenever it has been removed it has resulted in vigorous protest from our technical workers. In order to check the syringes we have one graduate for our laboratory standard and we compare each syringe used with this standard. It is presented as a time and labor saving device which substitutes mechanical precision for the inaccuracies inherent in the operation of pipetting by hand.

Discussion:

DR. MACNEAL: Is it possible to adjust the quantities which the syringe delivers?

DR. CORNWALL: Yes, it can be adjusted for any quantity up to the maximum content of the syringe.

PARAGANGLIOMA INTERCAROTICUM

EMIL SCHWARZ, M.D.

This specimen is about one half of the tumor because the surgeon thought it to be enlarged lymph glands. The tumor measured 8x3 cm. The surgeon noticed that there were branches from the carotid artery between the structures of the neck and an attachment of the tumor, so he had quite a difficult time in removing the tumor in his office. The tumor shows a greyish capsule and a whitish parenchyma. It presents the typical structure of a paraganglioma. So far as the surgeon says, the tumor was very well defined, having a smooth capsule. The man was operated on in December, and ever since then has been perfectly well, although the surgeon is sure that he left quite a number of particles of tumor between the structures of the neck.

It is noteworthy that I was not able to demonstrate the presence

of chromaffine tissue in the tumor, although I tried with Grenacher's carmine and with Giemsa's stain, according to the technique indicated in Schmorl. This stain should show a reddish violet protoplasm to chromaffine cells, but I was not able to demonstrate it. I see, however, from the literature that this happens very often.

TERATOMA OF THE TESTIS

EMIL. SCHWARZ, M.D.

This tumor is from a man thirty-three years of age, who had noticed a swelling of the testis for about a month. The tumor is very well defined, and showed on gross inspection signs that the tumor was composed of cartilage, bone, and various cystic cavities which might be lined with epithelial structures. Within the substance of the testicle, about 3 mm. distant from the well-defined tumor, one found a small fibrous nodule. The tumor, as it was very well defined, did not indicate malignancy.

Gross inspection indicated a teratoma and the sections confirmed the suspicion. As regards the malignancy of the tumor, I am sure that the proof of the presence of distinct carcinomatous tissue in the above-mentioned nodule, at some distance from the tumor, will leave no doubt that an epithelial portion of the teratoma is spreading as a carcinoma into the surrounding tissue.

I found in the sections a bronchus, also large intestine, goblet cells with high columnar epithelia. As regards small intestine, I am not sure that there were actual villi. There were, furthermore, smooth muscle cells, fibrous tissue, adult and embryonal cartilage, bone tissue, and a stratified layer of columnar epithelium going over into squamous epithelium (probably a "Mundbucht"). In certain portions it looks as if squamous epithelial collections with pearl formation were superimposed on columnar epithelium, so it suggests a metaplasia of a portion of the respiratory tract. At any rate, it is a totipotent teratoma, and does not come within the class of the Wilms tumor as I originally thought it to be when I saw the tumor. It is simply a teratoma with all the structures of the three germinal layers.

Discussion:

DR. WOOD: These teratomata of course are always fascinating to examine and permit a great scope to the imagination in diagnosing the various histological possibilities. Sometimes they form selective metastases. Of course, sufficient time has not elapsed in this case to determine that, but I recall one testicular teratoma in which the abdominal metastases contained striated muscle, an extremely rare occurrence. However, animal experiments often clarify human pathology. In the Crocker Laboratory there is a tumor arising from the sternum of a white rat which contains enormous quantities of striated

muscle fibers, plus some sarcoma. Interestingly enough, the transplants of this tumor after fifteen generations still show striated muscle fibers. This tumor is highly malignant, forming very large masses which often weigh more than the rat which carries it. Such animals seem to be otherwise in perfect health, and there is no clinical evidence of cachexia. I have been watching for about four years a patient with metastases from one of these teratomata, in which the metastasis is apparently largely of the cartilaginous portion. He has a very large and hard abdominal tumor which grows very slowly. He has no cachexia, only some shortness of breath due to pressure on the diaphragm. This enormous mass is a metastasis from a teratoma of the testicle removed five years ago. It resists radiation, showing it is not composed of highly sensitive cells, but is composed of the cartilaginous fraction of the tumor. One of the famous historical cases of so-called pure chondroma of the testicle with metastasis was reinvestigated and found to be a teratoma and not a chondroma, so that instead of it being a metastasizing chondroma, it was really a teratoid tumor.

DR. SCHWARZ: I saw metastasis of a teratoma of the ovary which plainly was of the neuroblastoma type, although at first sight one might have believed it to be a sarcomatous metastasis. Such apparent sarcomatous deposits from a teratoma are probably in many cases derived from neuroepithelium and embryonal nervous structures.

The explanation of such structures as cartilage in metastasis, as Dr. Wood pointed out, is extremely difficult, as such highly differentiated cell complexes are hard to explain when they metastasize. A lot of guessing and diagnosing of normal histological structures has to be done when teratoma or dermoids are examined histologically. It might be mentioned that the persistence of one structure is rather common in the literature, as, for instance, the well-known tooth of Saxer. In such cases, this one element develops often in a malignant way with the suppression of all other tissue elements.

AMEBIASIS IN RELATION TO ARTHRITIS DEFORMANS AND TO HODGKIN'S DISEASE

CHARLES A. KOFOID, PH.D., SC.D., L. M. BOYERS, M.D., AND
OLIVE SWEZY, PH.D.

*(From the Zoological Laboratory, University of California, Berkeley,
California)*

The discussion this evening insofar as it relates to arthritis deformans is based upon the work of Dr. Olive Swezy and Professor Kofoid in stool examinations for the past four years, in the course of which time we have found a number of instances

of coexistences of amebiasis of the bowel and of arthritis, the clinical type of which was, in most cases, unknown to us. Dr. L. W. Ely has recently (1920) distinguished a "second" type of arthritis, which is non-bacterial. Through his kindness we have been able to examine sections of the excised head of the femur preserved in formalin from his case 187. Thin sections of this bone were stained by us in iron hematoxylin and carefully searched. This preparation has revealed not only cells which we interpret (1922*a*) as amebæ, but also has enabled us to find (1922*b*) the supposed ameba in certain phases of mitosis.

The finding of these phases of mitosis enables us to bring forward the most convincing type of morphological proof that these ameboid structures are parasitic amebæ and not merely ameboid human cells. This conclusion rests upon the fact that the type of mitosis in the rhizopods generally and certainly in amebæ of the human digestive tract is a well-marked and peculiar one. It differs in three striking particulars easily recognizable in the proper phases of the process of mitosis from mitosis in the human cells. These phases are brief and prolonged search has been necessary to find them. The fixing of this tissue immediately upon excision has preserved intact in normal cytological condition these evanescent phases of cell multiplication of the ameba.

The three structural features which characterize the phases of mitosis in amebæ are the following. In the first place, the nuclear membrane remains intact throughout the whole process of mitosis. The daughter nuclei arise from the parent one by an equatorial constriction which divides the spherical parent into two spherical daughter nuclei. In the cells of the Metazoa, including those of man, the nuclear membrane disappears at mitosis.

The second characteristic is the presence inside of the nucleus of the centrosome, which in the resting stage lies in the central karyosome of the nucleus. In the prophase of mitosis this moves out against the nuclear membrane and divides into two daughter masses which then migrate to the poles of the nucleus about to divide. During the migration, there forms a deeply staining thread, black in iron hematoxylin stain, which joins the two

daughter polar masses and lies in a meridional position against the inner face of the nuclear membrane. This structure we have called the intradesmose in contradistinction to the paradesmose of flagellate mitosis which joins the daughter centrosomes of the flagellate nucleus. These centrosomes and the paradesmose both lie outside of the nuclear membrane in flagellates. In the case of the metazoan cells, including the human cells, neither intradesmose nor paradesmose is formed. The daughter centrosomes are connected in metazoan cells, if at all, by a cluster of fibrils, lying in the axis of the nuclear spindle and designated as the centrosmose.

The third distinguishing feature is the number of chromosomes which may be counted at the metaphase of mitosis. We have determined the number of these chromosomes in three species of the amebæ of man. In *Endamoeba coli* the number is six (Swezy, 1922). In *Councilmania lafleuri* the number is eight (Kofoid and Swezy, 1921). The number in *E. dysenteriae* (*E. histolytica*, Schaudinn), the etiological factor in amebiasis, is probably six. It does not seem to be in excess of seven or eight, nor less than five. We have not as yet found a sufficient number of favorably placed critical stages to enable us to state the exact number of chromosomes with the certainty with which we have determined it in the other species.

The number of chromosomes which the human cell exhibits in the metaphase of mitosis is, on the other hand, very much greater, appearing to be either twenty-four or forty-eight, possibly both, the former being the diploid and the latter the tetraploid condition. There is little probability of an experienced cytologist mistaking human cells at division with this large number of chromosomes for amebæ having the smaller number. In the light of this cytological and protozoological evidence, we conclude that parasitic amebæ are found in the lesions of Hodgkin's disease. The question at once arises as to whether they are the long-sought etiological factor of this disease or merely a coincident infection without causal relationship.

The cells which we interpret as amebæ in the bone marrow are clustered in the immediate neighborhood of the areas of

pathological activities in the head of the femur, lying just below the eburnated surfaces of the joint, and are not far distant from the hypertrophied bone tissue near the margin of the joint. They are more abundant about capillaries or small blood vessels. They are distinguished not only by pseudopodia, vacuolated protoplasm, and occasionally by evidence of food vacuoles, but also by the fact that the nucleus is relatively smaller than that of most human cells, except those of the eosinophiles, is more uniformly spherical, and has a peripheral film of chromatin attached directly to the nuclear membrane. If this peripheral chromatin is broken up into lobes, these lobes are usually smaller than those found in human cells, such as in the nucleus of the plasma cells. In addition, the nuclei of the amebæ have a solid, spheroidal granule or karyosome, usually central in location, although sometimes eccentric. The clear zone which lies between this karyosome and the peripheral chromatin is traversed by a few radial, deeply staining spoke-like threads. A narrow clear halo can be detected immediately around the central karyosome in some nuclei, but not in all.

The presence of the amebæ in the territory immediately around the lesions in the bone marrow and closely adjacent to the areas of eburnation and hypertrophy is indicative of the relation between the parasite and the lesions. While the cytological and protozoological evidence here presented is suggestive that the ameba is the etiological factor in Ely's second type of arthritis deformans, investigations along experimental and therapeutic lines are necessary to establish this hypothesis.

The relating of amebiasis to Hodgkin's disease is the result of the joint work of Dr. L. M. Boyers of the University of California Infirmary, Dr. Olive Swezy, and Professor Kofoid. (Kofoid, Swezy and Boyers, 1922*a, b*; Kofoid, Boyers and Swezy, 1922.) At the time of this communication, we have examined the stools thoroughly from seven patients suffering from Hodgkin's disease and have found amebiasis of the bowel in all seven. It is probable that Lincoln's (1908) case of Hodgkin's disease was also attended by amebiasis.

In sections of excised cervical and inguinal lymphatic glands

in cases of Hodgkin's disease, we have found ameboid cells which in nuclear structure, pseudopodia, and vacuolated protoplasm closely resemble cells which we have interpreted as amebæ of the bone marrow. They have similar spherical nuclei with peripheral chromatin, central karyosome, spoke radii and sometimes a halo about the karyosome. Prolonged search of an excised human inguinal gland (Walker's case) removed in what seems to be an early stage of the degenerative phenomena attending Hodgkin's disease, showed a considerable number of amebæ among which we have found certain ones in mitosis. The evidence in this case is similar in nature and extent to that in the bone marrow in the case of arthritis. These ameboid cells have the nuclear membrane intact during mitosis, exhibit an intradesmose, and have approximately six chromosomes.

The human tissue cells dividing in this same gland lose entirely, at mitosis, all traces of nuclear membrane, have no intradesmose, and have a larger number of chromosomes, certainly not less than twenty-four, nor more than forty-eight.

The distribution of the cells which we interpret as amebæ in the excised glands from cases of Hodgkin's disease is suggestive. They are found rather sparingly in and near areas of most active disintegration of the tissues. In some instances the appearance of the nucleus and the cytoplasm of the parasitic ameba is such as to suggest a moribund condition of the parasite. The cytoplasm loses its characteristic vacuolation, the body is rounded up, and the nucleus stains diffusely.

Extensive experimental and therapeutic investigations are necessary in order to establish the hypothesis that Hodgkin's disease is amebiasis of the lymphatic glands.

In the course of over 17,000 examinations of nearly 7,000 persons carried on at the Army Laboratory at New York City and in the Division of Parasitology, Bureau of Communicable Diseases, California State Board of Health, at Berkeley, we have found an unexpectedly high percentage of infection by *E. dysenteriae*, varying from month to month and averaging 16.5 per cent. Some of these persons had travelled in the Tropics, some (2,300) were soldiers who had had some overseas service, some

(576) were home service men (Kofoid, Kornhauser and Plate, 1919), and all of the others were under physicians' care for intestinal troubles, or were being diagnosed for more or less obscure complaints. It is very evident from the nature of our data that amebiasis is endemic in the United States, perhaps somewhat more generally than has hitherto been supposed. These facts as to the distribution and occurrence of this parasitic infection of the bowel of man afford a statistical basis for the occurrence of occasional sequelæ, not only of abscess of the liver, of the lung and of the brain, but, it may be, of amebiasis of the bone marrow and of the lymphatics.

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Discussion:

DR. WOOD: I wish Professor Kofoid had had time to tell many of the other interesting facts which he discussed while we were in my laboratory to-day. I think he has left no step untaken to eliminate any claim not based on pure observation, nor does he make any statement as to the necessary pathogenic relationship of these organisms to arthritis or Hodgkin's disease. Professor Kofoid has placed before us a very important observation, yet I feel that we will have to have very considerable training in order to identify these organisms and to search our material intelligently. Some of these ar-

thrititis cases have been well influenced by emetin, which of course suggests that the ameba may have some pathogenic relationships with the disease. That should be investigated, and all of this most arduous work which Professor Kofoid has carried out should be checked thoroughly, and it will be very interesting to see the suggestions he has made followed out, and if the relationship of these two obscure diseases can be settled, I think this is one of the most important presentations we have had before this Society in a long time.

DR. MOSCHCOWITZ: I happen to be rather familiar with Dr. Ely's material, for he allowed me to study his specimens histologically. There was one thing that impressed me, and that was the remarkable absence of any reactive zone around these areas of necrosis and cyst formation. It seemed to me it was in striking contrast to the remarkable reaction we obtain in Hodgkin's disease, and therefore I think it would be very difficult to explain the pathogenesis of the amebæ in relation to arthritis upon that score alone.

DR. KOFOID: In regard to the point raised, I will call attention to the fact that there was in the bone some distance from these areas a process of exostosis going on, and there was considerable change there. In the study of the lesions in the bowel, one is impressed by the fact that there are territories of considerable reaction of the tissues rather removed from the actual location of the ameba. I was impressed a great deal by the fact that you may hunt through large territories where the characteristic reaction of the tissues has occurred, and find no ameba, but in time you will come to a territory where they are abundant. We need a lot more study on the tissues of the bowel in amebiasis to get the true picture of the process that actually goes on. I think we also need much more help in the process that goes on in the bone. There are a great many puzzling things there, and I wish somebody who is a thoroughly competent student of bone marrow would publish something on the pathology and cytology of bone marrow in all its aspects with especial reference to animal parasites and bacterial infections, and also that we might have something on leucocytes in feces. It would help out the protozoologist very much indeed if somebody would tell us what changes leucocytes go through after they enter the lumen of the bowel. They are one of the pitfalls that beset the protozoologist, for certain eosinophile cells have nuclei strongly like the nuclei of amebæ.

EXTENSIVE DIFFUSE GROWTH OF THE CEREBRO-SPINAL PIA MATER

L. P. RAND, M.D.

(From the Pathological Laboratory, Bellevue Hospital, Dr. Douglas Symmers, Director)

The purpose of this paper is to place on record a case of primary diffuse growth of the pia arachnoid which appears to belong to a rare but well-defined pathological and clinical condition customarily classed as diffuse sarcoma.

The patient, P. McG., aged twenty-two, was admitted to the service of Dr. J. A. Hartwell, of the Second Surgical Division, Bellevue Hospital, on March 23, 1922, complaining of pain in the back, headache, and failing vision. He stated that, while a member of the A. E. F., at Soissons, September 17, 1918, he was thrown in the air by the concussion of a shell, fell on the flat of his back, and was knocked unconscious. On coming to, he found that he could not use his right leg. He was in a hospital for three months, regained the use of his extremity, and ran away to join his outfit. At the end of the war he received an honorable discharge and was well until January, 1921, at which time he developed the symptoms for which he came to the hospital. The pain in his back radiated down the right leg and was often preceded by numbness in the hips and legs. At the Polyclinic Hospital he was given a thorough orthopedic examination, and limitation of flexion of the lower dorsal and lumbar spine was found. X-ray examination showed a faint irregularity between the fourth and fifth lumbar vertebræ, which was diagnosed as an old dislocation. There was also a bilateral papilloedema. He was given a brace which, however, did not relieve him, and he was admitted to Fox Hills Hospital in August, 1921. At that time physical examination revealed nothing new. There were no clear-cut localizing motor, sensory or reflex changes. The cerebrospinal fluid was under decreased pressure, but was otherwise negative, except for a luetic colloidal gold curve on one occasion; the Wassermann reaction was negative. The patient was surly and uncommunicative. Because of the rapidly increasing papilloedema, a subtemporal decompression was performed by Dr. King, which temporarily relieved the vision. No evidence of tumor was found. The papilloedema recurred, and a larger decompression was done, with the removal of a bone flap in the left parietal region. Aphasia and right-sided paralysis developed, but cleared up in two months. Herniation of the brain gradually took place through the bony defect, and from this time on many surgical measures were taken to relieve the increased intracranial pressure, including needle puncture aspirations through the hernia, which gave such relief that the patient continually asked for more. Intensive x-ray treatment was given to check the suspected tumor, and hypertonic salt solutions were given intravenously, as suggested by Cushing, to relieve the intracranial pressure. Ventriculography showed a definite bilateral internal hydrocephalus. Air injected through a lumbar tap was shown by x-ray to pass through the foramen into the subarachnoid spaces under the base of the brain. Another operation was performed, the left ventricle explored, and the region of the aqueduct palpated. No tumor mass was felt, and it was believed that the obstruction was subtentorial. A final operation (April 5, 1922) through an occipital opening revealed a dilated fourth ventricle and a patent aqueduct of Sylvius. The spinal fluid was seen to be clear, while that in the ventricle was deep yellow. However, no obstruction could be found at the foramen of Magendie. Two days later, aspiration through the hernia cerebri to relieve further accumulation gave a cloudy fluid from which a Gram-positive bacillus was obtained. The patient died on April 7, 1922.

Necropsy findings: The postmortem examination was essentially negative, except for the head and spinal cord. The head had been shaved for opera-

tion. In the left parietal region there was a horseshoe-shaped scar, well healed, the convexity upward. Here the skin was rather loose and could be felt to overlie a large bony defect. Over the lower occiput was a T-shaped incision overlying a bony defect removed at a recent operation for suboccipital decompression. An elliptical piece of skin, about 8 cm. across was left adherent to the dura over the parietal bony defect. Aside from this, the calvarium was removed in the usual way. The dura was apparently normal, except where firmly adherent to the skin in the parietal region and where incised at operation in the occipital region. The convolutions of the brain were considerably flattened. There was no increase of fluid over the hemispheres. Extending over a large portion of the basal surface of both hemispheres were partially confluent, grayish-white, rounded, slightly elevated plaques, up to several cm. in diameter, and from 1 to 2 mm. in thickness. The largest accumulation of tissue was over the optic chiasm. The pituitary appeared normal. Over the foramen of Magendie, the arachnoid was slightly thickened, and at one point had been incised at operation. At the site of the parietal defect was an area of cortex, the size of the palm of the hand, which bulged slightly and felt cystic. Here the dura was firmly adherent to the brain. The brain was placed in 10 per cent. formalin, at room temperature, and cut at the end of ten days. The left lateral ventricle was markedly, the right and third moderately, dilated. Beneath a pouched-out area of cortex was a large irregular cavity in the brain substance which communicated with the left lateral ventricle. This cavity and the ventricles were lined by yellowish granulation tissue and contained turbid yellow fluid. The fourth ventricle was perhaps slightly dilated; its ependyma was smooth. The aqueduct was completely plugged by soft grayish tissue. The substance of the brain was riddled with small and large cavities with clean-cut walls, so that the cut section resembled Swiss cheese. The brain tissue adjacent to these cavities appeared altogether normal.

The spinal dura appeared normal. On opening it, the subarachnoid space was found to be distended by pinkish-gray tissue which formed a more or less complete mantle about the cord throughout its length, partially filling the spinal canal. In some portions it was 3 mm. thick. In the cervical and lumbar regions it formed an incomplete covering. Everywhere the development was greatest over the posterior aspect of the cord. There was one discrete, oval plaque, 1x2 cm., on the dorsal surface of the cauda equina. Over this level there was a little clear (?) cerebrospinal fluid. The tumor tissue was soft and homogeneous, and extended along some of the spinal nerves into the foramina.

Microscopical report: Sections through the growth covering the cord and brain show a highly cellular tumor filling the pia-arachnoid space, surrounding the spinal nerve roots and sending prolongations into the processes of the pia in the cerebral convolutions. There is no infiltration of the brain or cord proper. The tumor consists of irregular bundles of varying size, made up of rather closely packed spindle cells. Their nuclei are of medium size, round or oval on section, and stain deeply. In some areas there is considerable variation in size and staining power. No mitotic figures are seen. These bundles

are separated by a loose fibrillar and reticular stroma, taking a pale eosin stain (apparently edematous connective tissue). In many areas the tumor is highly vascular, being rich in capillaries and larger vessels. In some places the tumor cells are thickly placed around the periphery of a medium-sized blood vessel, but this is not a prominent feature of the growth. The bundles of tumor cells lie in intimate relation to the nerve bundles, but there is no apparent connection. Scattered throughout the tumor are areas where the vessels are filled with polynuclear leucocytes, and the surrounding tissue shows a dense or scattered polynuclear infiltration. There are other areas in which are seen groups of large mononuclear cells filled with granular, brownish pigment.

The ependyma of the ventricles is thickened and densely infiltrated with polynuclear leucocytes. Sections of this membrane, stained by the Gram-Weigart method, show Gram-positive bacilli in large numbers, morphologically resembling the Welch bacillus.

Section of the wall of one of the cysts in the white matter of the cerebrum shows closely packed bacilli, similar to those seen in the ependyma, lying in a dense layer close to the cyst border. The nearby vessels contain many polynuclear leucocytes, but there is no other apparent tissue reaction.

Section through the aqueduct of Sylvius shows it to be occluded by recent granulation tissue, densely infiltrated with polynuclear leucocytes and bacilli.

The cysts in the brain substance are apparently "gas cysts" caused by the postmortem invasion of Gram-positive bacilli. It will be recalled that the brain was put intact in formalin, in a warm room, and it is assumed that the cysts were formed before the fixative reached the interior.

I have been able to collect ten cases in the literature of extensive primary diffuse tumor of the meninges (Schultz, Coupland, Hadden, Fox, Virchow, Olivercrona, Nonna, Schroeder, Busch, Markus). If we add to these the cases of sarcomatosis of the meninges where a primary tumor was found elsewhere in the central nervous system with extensive secondary meningeal infiltration, the number is increased to over thirty. As these cases show a similar clinical course and pathological anatomical distribution, they may be included here. The age limits were four to fifty-seven, but the great majority were under thirty. The duration of the disease is usually a matter of months, only two lasting longer than a year. A definite history of trauma was present in several, as in the case here recorded. The clinical course is varied because of the diffuse character of the lesions. In those cases where a large primary tumor was present, local pressure symptoms predominated. Most of the cases simulated a

chronic meningitis, the more acute cases being diagnosed as tuberculous or syphilitic meningitis. Pain in the head and back is an early symptom, often pain and hyperesthesia in the extremities. Later, muscular weakness and paralysis set in. Papilloedema is common, and occasionally there are ocular palsies. In two of Rindfleisch's three cases there was xanthochromatic cerebrospinal fluid and a high albumen content. This finding has been observed by others.

The autopsy findings in the various cases show a remarkable similarity in the matter of the distribution of the growth. In every case the process consisted of nodular or diffuse infiltration of the pia by a soft, yellowish or grayish pink growth which covered the optic commissure, the inferior surface of the cerebellum, medulla and pons, and passed down the spinal cord, thinly developed, if present at all, in the cervical region, and most marked in the thoracic and lumbar cord. This distribution may possibly be due to the scant room for growth in the region of the cervical enlargement. The growth is almost entirely along the dorsal surface of the cord, though sometimes encircling it. The investing layer is sometimes 1 cm. thick posteriorly. This distribution has but slight variations in all the cases. There is little or no tendency to invade the cord or brain, but the growth may infiltrate the pia mater, even to its final processes. It usually passes out along some of the nerve roots to the foramina. Cerebral involvement causes hydrocephalus in many cases. The only case of true primary meningeal sarcomatosis that metastasized was Olivercrona's case, where nodules were found in the liver and one kidney. The usual method of extension is evidently by the transfer of cell groups, shown by the miliary nodules at the margins of the tumor.

The microscopic findings are rather unsatisfactorily interpreted. The origin of the tumor, if there is a common origin, is obscured by the activity of the growth. Of eighteen cases, six were called small round-cell sarcoma, four spindle-cell sarcoma, one melanosarcoma, two gliosarcoma, two endothelioma, two perithelioma, and one angioblastic sarcoma. There is commonly a multitude of small blood vessels surrounded by tumor cells

in a perithelial arrangement. Ewing believes that this type of growth is best provided for under the designation of diffuse angioblastic meningeal sarcoma. It is believed that probably most of them arise from the endothelial or perithelial cells of blood vessels, or from the endothelium of the pia arachnoid. Certainly the macroscopic picture is a distinct and constant one, and the condition furnishes a clear-cut, well-defined pathological entity.

Discussion:

DR. WOOD: Without microscopical evidence I should be inclined to interpret this lesion as an organization of an extensive hemorrhage following the shell contact in France. It is very interesting. In the gross it would be very difficult to differentiate it from some such lesion. Even the differential microscopic diagnosis between sarcoma and connective tissue hyperplasia is not easy in lesions of this type.

DR. CORNWALL: May I ask if the literature made any mention of antecedent trauma?

DR. RAND: When the cord was taken out at autopsy we did not know whether the lesion was tumor or an excessive inflammatory process, and it was not till the microscopic section was seen that we reached our opinion. However, LeCount, in a personal communication to Dr. Symmers, expressed the belief that these lesions are very possibly inflammatory. I think it was Hadden's case that was reported as a chronic meningitis, but later observers consider his case a sarcoma. The slides of our case need further study, but all of us who have examined them consider the process neoplastic.

I recall two cases in which there was a history of trauma.

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A CASE OF PRIMARY CARCINOMA OF THE URETER

JOSEPH F. MCCARTHY, M.D., AND L. H. MEEKER, M.D.

ABSTRACT

The rarity of primary carcinoma of the ureter prompts the presentation of this case. This brief abstract is to be followed at a later date by a more detailed and comprehensive study of the case.

The patient, R. G., a male forty-nine years of age, was admitted to the New York Post-Graduate Hospital on May 7, 1922. The chief complaint was intermittent pain for four months in the right hip, radiating to the inguinal region. Physical examination was negative except for some resistance in the right hypogastrium. The usual laboratory tests revealed nothing of particular diagnostic significance. The outstanding fact was the obstruction of the right ureter seen by radiographic and cystoscopic examinations.

A tentative diagnosis of ureteral calculus was made and exploratory operation advised. The patient desired the operation postponed, and left the hospital. He re-entered the hospital on June 14, 1922, but was in such poor condition that operative procedure was out of the question. A cord-like mass was palpated, and malignancy of the colon or ureter was suggested. The patient died on July 8, 1922.

Autopsy revealed a tumor mass that encircled the ureter for its entire length, 65 mm. in diameter. Metastatic nodules were found in the liver, lungs, spleen, kidney, pancreas, omentum, heart, skin, etc. Microscopic examination showed the origin of the new growth to be from the epithelium of the ureteral mucosa. Papillary formations filled the lumen of the ureter, and at their base the tumor cells infiltrated all layers of the wall. Metastases were identical with the primary growth.

A diagnosis was made of advanced primary carcinoma of the ureter with extensive metastases.

Discussion:

DR. SYMMERS: Did you find anything in the literature comparable to this?

DR. MEEKER: There are reports of 16 authentic primary papillary carcinomata of the ureter, and I think also 4 of squamous celled carcinomata.

DR. EWING: I have been examining the specimen and puzzling over the diagnosis. It seems to me that on account of the size of the tumor and its relations conclusions are rather difficult to draw. Of course the clinical history is rather unfavorable to the diagnosis of primary carcinoma of the ureter. I would like to hear the opinion of the surgeon. The tumor undoubtedly shows transitional epithelium, of which there are many areas. The absence of a definite source in any other organ and the extensive involvement of the ureter would seem to lead by exclusion to the idea that it must arise

in the ureter. One of the most remarkable features of the case is the very active growth and the hemorrhagic character of the "red" portions, so-called, and also the reproduction of this hemorrhagic character due to the many dilated blood vessels in the numerous metastases. The body was literally riddled with metastases. I think Dr. Meeker's conclusion is correct. She has a very remarkable case of extremely extensive generalized primary carcinoma of the ureter.

DR. MCCARTHY: I recently presented six cases of papillary new growths of the renal pelvis, one of which involved the ureter, and in all of which there was hematuria. It seems to me that the papillary nature of the growth might lead to the conclusion that it did take its origin in the ureter. We urologists are apt to be a little conceited about our certainty in diagnosis until we encounter a case of this type. When this case first came under observation there was more or less well-defined tenderness in the region of the appendix; we thought of the possibility of a new growth of the colon, but as you noticed in the *x*-ray reports, there was so much distension with gas that no one of the pictures was satisfactory. Another interesting thing was the absence of pus in the urine. One would rather expect pus and blood in the urine in a case of this type, and it is this type of case which offers great difficulties in the way of diagnosis, short of exploratory operation. Where we can make a ureteropyelogram the diagnosis is relatively simple. In my opinion the case is definitely one of primary new growth of the ureter. I had never encountered a case like it before, nor heard of one for that matter, until Dr. Robin, one of our best investigators at the Academy, brought us case reports from everywhere. I think there were twenty-odd cases, some of which were not primary, but probably fourteen or fifteen of them were definitely primary new growths of the ureter, not taking their origin in the renal pelvis, but definitely in the ureter.

DR. MEEKER: I would like to call attention to the fact that no tumor previously reported is anywhere near as bulky as the one presented here.

XANTHOMA (XANTHELASMA) OF THE TONGUE

ELI MOSCHCOWITZ, M.D.

The patient, aged thirty, presented himself to Dr. Walter M. Brickner because of a tumor of the tongue which he had noted for some months. It was on the dorsal surface, round, hard, slightly elevated, yellowish, and about 1 cm. in diameter. The tumor was removed without trouble.

Microscopically the tumor presented a most unusual appearance which was frankly puzzling. I am indebted to Dr. F. C. Wood, who finally established the diagnosis of xanthoma. The growth lies at some distance beneath the epithelial layer from which it is separated by normal muscle fibers. There is no capsule, the xanthomatous tissue spreading irregularly into the surrounding muscle structure. The tissue consists of extremely large pale cells with a finely granular protoplasm staining faintly blue with hematoxylin. They

are irregularly round or oval, the cell outlines are faint and tend frequently to merge together so that great irregular granular syncytial plaques are common. The whole structure makes one understand the designation "foamy tumors" that has been applied to this tissue. Sharply staining, large, oval or quadrilateral nuclei are abundant, but their relation to individual cells is often indeterminate. In general they appear most abundant on or just beneath the cell membrane. Of significant interest is the fact that the structure is not homogeneous. Scattered throughout the tumor are numbers of muscle fibers, in bundles and individually. Close study with the higher powers shows distinct xanthomatous degeneration of the muscle fibers. An intact muscle fiber can be seen gradually to lose its striated appearance; the distinct eosin pink of the fiber gradually merges into the faintly blue xanthomatous tissue. At the same time the fiber swells appreciably and the delicate sarcolemma becomes the outline of the xanthomatous cell. The muscle nuclei become slightly smaller, but do not otherwise partake greatly in the change. Not infrequently one recognizes a large longitudinally placed xanthoma cell containing a small segment of well-stained muscle fiber showing the gradually xanthomatous degeneration on either end. In a sharply defined muscle bundle, one portion shows xanthomatous degeneration; the remainder is intact.

According to all morphological criteria, therefore, this "tumor" represents a xanthomatous degeneration of muscle fibers. The term "xanthoma" is divided by dermatologists into two varieties, xanthoma planum or palpebrarum, and xanthoma multiplex. Inasmuch as the latter presents itself as hard nodules the term "tuberosum" has been added. Xanthoma palpebrarum is familiar in elderly people on the eyelids, especially near the inner canthus, forming the so-called chamois-like deposits. Xanthoma multiplex or tuberosum is rare, and is present on various portions of the body, especially around the exterior surfaces of the elbows and knees, the palms, the trunk, and even the eyelids. Lesions have been described in the internal organs, the mucous and serous membranes, tendons, trachea, esophagus, liver, heart, aorta and spleen. It frequently begins early in life and is sometimes congenital and, according to Fletcher, four-fifths of the cases are accompanied by chronic jaundice. Diabetes is also not an uncommon accompaniment. The so-called xanthoma diabeticorum is not a separate variety of the disease.

For many years the lesions of both xanthoma palpebrarum and multiplex were considered identical. Both were supposed to be the result of a fatty or lipoid degeneration of connective

tissue structures. We are indebted to Pollitzer, who has made some of the most important contributions to the study of xan-

FIG. 1. LOW POWER.

thoma, for a sharp differentiation between the two lesions. Pollitzer showed that xanthoma multiplex is the result of a xan-

thomatous infiltration of the adventitial connective tissue cells of the papillary and subpapillary layers of the skin which take up

FIG. 2. High power.

lipoid substances from the blood vessels. In xanthoma palpebrarum, on the other hand, the lesion consists in a xanthomatous de-

generation of the fibers of the orbicularis muscle. The specimen which I present seems therefore to be most unusual and histologically must be classified as a "xanthoma planum."

The manner whereby xanthomatous tumors are formed is a much debated and perplexing subject. It seems to be well agreed that the xanthomatous material exists in the form of a cholestero-fatty acid-ester. Pollitzer makes the explanation that this substance is present in the blood in excess in cases of jaundice and diabetes and is deposited in cells in those situations where friction and trauma are most likely to occur. However, Rosenbloom and Rosenthal and Braunisch in a very recent study failed to find a cholesterinemia in xanthoma multiplex.

Xanthoma of the tongue is rare. Butlin, in his work on "Diseases of the Tongue," describes a patient who was jaundiced and presented numerous xanthomata. On the side of the tongue were two yellowish oblong patches, raised, soft and varying in size from a pea to a sixpence. Smith in 1912 reported another case similar in structure to the one here reported. These are the only cases I have been able to find.

Discussion:

DR. POLLITZER: Xanthoma has attracted very little attention on the part of general pathologists; the condition is rare, and in general of very little importance. Perhaps it is for this reason that the confusion between what is called xanthoma tuberosum and xanthoma planum that arose from the unfortunate association of the two forms in one of the first cases described by Addison in 1850 has gone on down to the present time. Practically all the books on dermatology and pathology adhere to a subdivision into two forms, the tuberoso, or generalized, and the plane, or palpebral form. And yet the clinical differences between these two conditions are so striking that on clinical grounds alone it seems to me obvious that the two processes have nothing in common except a yellow color. Xanthoma occurs as prominent, hard, round, or lobulated tumors; xanthelasma (a name I have suggested should be used distinctively for the plane form) is a flat, soft discoloration, indistinguishable on palpation. Xanthoma occurs at any period of life, but usually in early adult life and childhood. It develops rapidly, in a few weeks or months, disappears after months or years, or undergoes fibrous changes and persists indefinitely. Xanthelasma is practically unknown before middle age; its development is slow, extending over years; once established, it persists throughout life; it never undergoes fibrosis. Xanthoma is extremely rare; xanthelasma quite common. The lesions of xanthoma occur anywhere on the general integument with the

neighborhood of the large articulations as the seat of predilection. (Under the tense epidermis of the palms the tumors may be spread out in striæ along the normal folds.) Xanthelasma is limited to the face and neck, the region of voluntary cutaneous muscles, and in rare instances has occurred on the tongue, the uvula, etc.

Histologically, xanthoma is an irritative connective tissue cell hyperplasia due to the presence of cholesterol fatty-acid esters derived from the blood. The process begins with the extrusion of cholesterol into the vascular adventitia whose cells take up the lipoid particles, increase in size and proliferate, sometimes becoming multinucleated. The cells, arranged in masses around a blood vessel, act as stimulants to the production of fibroblasts, resulting in old xanthomas in the development of fibromas which have been erroneously interpreted as the primary tumor, xantho-fibroma. Xanthoma connotes a systemic disease, a disorder of metabolism of which cholesterolemia is the most obvious symptom. The fact that different observers have reported discordant results in their estimation of cholesterol in the blood in these cases may readily be accounted for on the ground that the cholesterol may be present in excess only during the stage of active formation of the little tumors, which will persist, however, after the cholesteremia which occasioned their development has disappeared. It is nevertheless a fact that extremely high figures for cholesterol in the blood have frequently been recorded in these cases, 6 grams or more per thousand.

In xanthelasma on the other hand there is no evidence of a metabolic disturbance. The highest figures recorded in simple cases of xanthelasma are just about on the upper level of the normal for cholesterol, 1.90 per thousand. Histologically there is no sign of connective tissue or other inflammatory change. In studying the histology of xanthelasma I earnestly advise that the anatomy of the normal eyelid be studied first. In the normal eyelid there is an extensive layer of striated muscle fibers filling the space between the epidermis and the subcutis. In old cases of xanthelasma this layer of muscle fibers has almost completely disappeared and in its place we find the so-called xanthoma-cells and masses. It is only in recent cases of xanthelasma that the relation of muscle fibers and "xanthoma" cells can be clearly made out. In early cases we find abundant muscles showing degenerative changes; the fiber loses its striations, becomes glassy in appearance, sarcolemma nuclei proliferate, the muscle substance becomes clumped, and takes stains irregularly; finally fatty particles are disclosed and the muscle breaks up, the sarcolemma sheath however persisting. These changes frequently may be followed in a single fiber cut longitudinally and most of them are beautifully shown in the sections of xanthelasma of the tongue before you under the microscope. The few cases of this peculiar degeneration occurring on the tongue, the uvula and in one case in a congenital pendulous myoma have been regarded as xantho-myoma. The term implies a tumor of the muscle fibers, but as a matter of fact, there is no increase of muscle fibers in these cases, but on the contrary, as is obvious in the eyelid lesions, a disappearance of muscle fibers.

In conclusion, I should like to say that there is no ground for the current

subdivision of xanthoma into two forms, planum and tuberosum. These two conditions are totally distinct processes, the one a connective tissue pseudotumor, the other a focal degeneration of striped muscle fibers. For the one the name xanthoma may be retained; for the sake of clarity the other should be given a different name. I have proposed that the name xanthelasma be retained for the myogenetic form. The case shown by Dr. Moschowitz is not a xanthoma, but a xanthelasma of the tongue.

DR. ROHDENBURG: In a case of hemachromatosis in a female, who quite incidentally developed a series of xanthomata on the eyelid and in various portions of the face, the diagnosis being confirmed by removal of some of the specimen, during the acute stage this woman had a blood cholesterol of 800 mg. per 100 c.c. of blood. About three weeks after the acute stage had subsided she had a blood cholesterol of 250 mg.

DR. SYMMERS: Incidentally hemachromatosis in a female is an extremely rare phenomenon.

CARCINOMA WITH GRAVE ANEMIA

A. V. ST. GEORGE, M.D.

(From the Pathological Laboratory, Bellevue Hospital, Dr. Douglas Symmers, Director)

The following case presents a rather interesting and by no means undisputed clinical condition.

The patient, a white male, fifty-seven years of age, nationality Swedish, occupation stableman, was admitted to Bellevue Hospital in May, 1920, when a diagnosis of pernicious anemia was made. At that time he had lost weight and presented the typical blood picture of pernicious anemia. He was re-admitted on March 12, 1921, and stayed in the hospital until March 31st, when he was again discharged, at his own request, condition unimproved. On May 24, 1921, he was again admitted to the hospital with the following history:

Since the previous admission, he had not felt well at any time, and recently had developed pain in both legs and in the right chest; he did not work for five weeks. Weakness, emaciation and dyspnoea were the chief symptoms.

Physical examination showed a thin, emaciated male, of pale yellow complexion, who looked chronically ill. The mucous membranes were very pale; eyes, nose, mouth, neck and lungs were negative. The heart showed a diffuse apex beat in the fifth interspace, 9.5 cm. from the mid-sternal line. The heart was not enlarged. Diastolic blowing replaced the first sound and followed it at the apex. There was a systolic blow at the pulmonic area. The heart was regular in rate and rhythm. The abdomen was negative. The arteries were thick and beaded. Examination of the eye grounds showed the discs pale; there were old and new hemorrhages in both eyes.

During the patient's stay in the hospital he became progressively weaker and, during the last days of life, he was partially irrational. The pulse ranged

from 114 to 130; temperature from 97 to 98.4. The urine was negative; the Wassermann reaction was negative. The red count was persistently low, with a low leucocyte count. On the last day of life the count was as follows:

| | |
|--------------------------------------|---------------------|
| Hemoglobin..... | 10 per cent. (Dare) |
| Red cells..... | 460,000 |
| White cells..... | 2,000 |
| Polymorphonuclears | 40 per cent. |
| Lymphocytes..... | 51 per cent. |
| Many normoblasts and poikilocytosis. | |
| Polychromatophilia. | |
| No megaloblasts seen. | |

Gastric analysis showed no free hydrochloric acid. The clinical diagnosis was pernicious anemia.

Autopsy No. 7343: The body was that of an emaciated white male of good development, five feet, nine inches in length, weighing about 110 pounds. The subcutaneous fat was very scanty and lemon-yellow in color. The heart was large and flabby and contained thin fluid blood. There were no changes in the valves. The myocardium was yellowish and friable. A network of yellowish striations was visible under the endocardium—the so-called tiger striping. All the chambers of the heart were dilated. The kidneys were slightly enlarged and, on cutting through the capsule, the kidney substance bulged. The pelves were filled with a large amount of lemon-yellow fat, and the markings were largely obscured. The liver was normal in size, somewhat reduced in consistence, and had a yellowish color. There were no signs of siderosis. On the mucosa of the greater curvature of the stomach, two inches from the pylorus, was a soft, irregular mass, about one inch in diameter and extending into the stomach for three-quarters of an inch. The surface of the most prominent portion was covered with dark red blood and appeared ulcerated. For a distance of one or two cm. around the mass, the mucosa appeared thickened; elsewhere it was normal. The bodies of the vertebræ contained considerable red marrow. The long bones could not be opened in this case.

Anatomical Diagnosis: Dilatation of heart; fatty degeneration of myocardium (tabby-cat heart); hydrothorax (bilateral); partial atelectasis of lungs; old tuberculous nodule of right lower lobe; edema of visceral pleura; chronic parenchymatous nephritis; fatty degeneration of liver; adenocarcinoma of stomach; atheroma of aorta; red bone marrow; anemia of pernicious type.

Histology: Microscopic examination of the growth from the stomach showed a typical well-formed adenocarcinoma with ulceration.

Pernicious anemia as a distinct clinical conception in association with carcinoma of the gastro-intestinal tract has been reported both in the foreign as well as in our own literature. In the reported cases, a small ulcerating carcinoma of the stomach was generally an accidental finding at autopsy. But whether the

carcinoma is the primary disease and produces the picture of pernicious anemia, or, secondly, whether it is merely incidental and coexistent, or, thirdly, whether we assume that the achylia gastrica of pernicious anemia prepares, so to speak, the gastric mucosa for the development of a carcinoma, is a problem still unsolved. Can a carcinoma produce an anemia of such magnitude as to give a blood picture of pernicious anemia? The answer must be yes. Cabot, in discussing this question, presented a series of gastro-intestinal cancer cases in which there was no anemia whatever. He states that whenever the anemia in carcinoma attains a picture simulating the pernicious type, we generally find leucocytosis and relatively few, if any, megaloblasts. It will be noted that in our case no leucocytosis was encountered. In the differential diagnosis of the two conditions, Cabot urgently advises not to make the diagnosis from the blood picture alone.

Recently Hartman reported a case in which blood changes simulating pernicious anemia developed in a gastrectomized patient (gastrectomy for carcinoma). He also refers to one other case reported by Moynihan. He suggests, in view of this experience, that the absence of the gastric enzymes may play a rôle in the production of pernicious anemia.

In an interesting study of the anemias accompanying carcinoma, Roessingh found that new growths arising from skin or mucous membrane invariably showed an anemia. New growths in other structures followed no such rule. He quotes Verse, who in an accidental finding of twelve tumors of the gastro-intestinal tract, none of which measured larger than 11 mm. in diameter, stated that four showed macroscopic and the remainder microscopic ulceration. Statistics indicate that at least 92 per cent. of intestinal new growths give a positive chemical reaction for blood in the stools. The presence of blood in the feces in a case of suspected pernicious anemia is, therefore, of importance. Roessingh further attaches great weight to the determination of the bilirubin content of the blood in carcinoma and states definitely that, except in cases where there is a primary or metastatic new growth in the liver causing obstruction to the

bile flow, there is never an increase in the bilirubin content of the blood, and hence there can be no real blood destruction. Unfortunately, this was not determined in our case, though experiments now in progress with the test tend to confirm Roesingh's results.

It is interesting to note that in all reports of pernicious anemia with an accompanying tumor, the tumor was located in the gastro-intestinal tract.

In conclusion, it cannot be definitely stated whether carcinomata of the gastro-intestinal tract produce a blood picture simulating pernicious anemia. From the fact that practically all gastric carcinoma patients present a constant melena and that repeated small bleeding of experimental animals produces an aplasia of the bone-marrow, it is conceivable that this factor alone, and quite independent of carcinoma toxins or gastric atrophy, exhausts the bone-marrow to such an extent as to produce a pernicious anemia picture. How long the patient in our case had the tumor is also not determinable.

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ROESSINGH, M. J.: *Deutsches Archiv f. klin. Medizin*, 1922, cxxxix, bd. 5 and 6.

Discussion:

DR. STILLMAN: I think the point Dr. St. George has emphasized is important, that a definite diagnosis of pernicious anemia may be extraordinarily difficult. The blood picture in these primary carcinomata of the gastro-intestinal tract is at times identical with that found in pernicious anemia. I do not know whether I quite understood Dr. St. George to suggest that the anemia might be due to hemorrhage from the tumor. It seems to me that it is difficult to accept that. The work that has been done recently at the Rockefeller Institute in regard to the changes which take place in the bone marrow following repeated hemorrhages shows that it requires more than simple loss of blood to produce the activity of the bone marrow we find in pernicious anemia, and that we find also in these cases of tumor. It is more than loss of hemoglobin. Apparently there is a toxic factor in addition. I think Dr. St. George is quite right in saying that the diagnosis of pernicious anemia here is an exceedingly questionable one, and it is much more probable that the anemia is associated with the tumor growth.

DR. FRIEDMAN: I believe that if repeated bleeding alone could be the cause of pernicious anemia, you would see in carcinoma the picture of pernicious anemia more frequently. I remember one case in my student days which was diagnosed by Dr. Staddman as pernicious anemia, and at the autopsy by Professor Thoma a carcinoma in the posterior wall of the stomach was found. I do not know what the examination of the bone marrow showed, but pernicious anemia is very frequently confused with carcinoma. As to achylia gastrica, I do not believe that it predisposes to carcinoma. I have seen a number of achylia gastrica cases. Some of the patients I have examined ten or twelve years later, and I have always found the same condition of achylia gastrica. I do not remember in all of my cases that any one of them developed carcinoma or pernicious anemia while they had achylia gastrica.

DR. MOSHCOWITZ: It seems to me that the question is entirely academic as to whether the patient had primary pernicious anemia, or whether he had carcinoma with the clinical picture of pernicious anemia. There is no doubt but that the blood picture characteristic of pernicious anemia can be caused by definite known things, *e.g.*, the *Bothriocephalus latus* infection. There is also no doubt but that carcinoma of the stomach can give the identical picture. The only reason why we make a differentiation is because we know the cause of one, and we do not know the cause of the other. Primary pernicious anemia is only called "primary" because we do not know the cause. I think the wisest point of view is to regard pernicious anemia as a syndrome which may be due to a definite and to an unknown cause.

DR. DENTON: In regard to the bleeding in pernicious anemia, Dr. René Mouchet and myself reported a case of two negroes in the Belgian Congo, who were really property of the Government. We wanted to decide whether they had sleeping sickness or not. We drew twelve c.c. of blood from each of these two patients every day for thirty-four days. At the end of this period we became alarmed at the appearance of the two negroes and examined their blood. One of them, an apparently normal negro with the exception of the suspicion of sleeping sickness which was not in any sense certain, developed a typical picture of pernicious anemia with both large and small nucleated red cells. The quantity of blood taken out of the man was not large as compared with what is drawn in transfusions, when they take from 1,300 to 1,500 c.c. of blood at one time. The other negro did not show the nucleated red cells, but he did show a rather marked anemia for the amount of blood which had been taken out. I admit that this is not definite, because of the countless negroes that we autopsied over there nearly all showed hookworm. That is one possibility that we could not exclude, but there was a great difference in the appearance of the two men after taking twelve c.c. of blood from each of them for thirty-four days.

DR. SYMMERS: What happened when you ceased taking the blood?

DR. DENTON: They became all right again.

DR. EWING: This discussion brings up the question, what is the essential element in pernicious anemia? I am rather interested to hear in the New York Pathological Society, which is devoted to the study of pathological

anatomy, a discussion which fails to consider the essential lesion of pernicious anemia in the bone marrow, and I think that the whole discussion would be cleared up if one recognized, what I believe to be the truth, that pernicious anemia consists of an abnormal formation of blood in the bone marrow, and that when we can demonstrate histologically this abnormal formation of blood in the bone marrow we have established the diagnosis of pernicious anemia. Therefore I think that we must have a report of the bone marrow in this case. There may be quite a variable picture in the bone marrow of pernicious anemia, and we have not this evidence in the case presented. It is clear that pernicious anemia sometimes follows hemorrhages. Progressive fatal anemia is not so very infrequent with bleeding carcinoma in various parts of the body.

DR. ST. GEORGE: It is a well-established fact that investigators, after taking about five c.c. of blood from animals for about two weeks, have produced the blood picture of an anemia of the pernicious type. I think the same picture is probably to be seen in any case of carcinoma, provided the disease has lasted sufficiently long. Whether it is produced by a toxin derived from the growth, I do not think anybody can answer. In this case none of the clinicians who saw the patient thought of a carcinoma. If this small growth had been taken out, the patient's life might possibly have been saved, provided he did not have a true primary pernicious anemia.

CARCINOMA OF THE APPENDIX: FIBROSARCOMA OF BACK: ADENOCARCINOMA IN CURET- TINGS OF UTERUS

D. S. D. JESSUP, M.D.

The specimens for demonstration were thought to have features of sufficient interest to warrant their presentation to the Society.

The first specimen is an appendix removed in the course of a routine operation in a case of cholecystectomy. The patient was a physician, sixty years old, who had always been in good health and had had no surgical or medical diseases except an attack of gall stones some thirty years before. The appendix on examination appeared like a normal appendix, and it was only on microscopical examination that we came across a rather unusual picture. Microscopically the mucosa is entirely replaced by a growth of large, irregular glands, with entire loss of the normal structure of the mucosa and the lymphoid tissue, so that everything is destroyed out to the muscularis. This is not invaded. The cells are filled with mucus, and with different stains give different appearances. With a deep hematoxylin stain they look very dark in color, and with a light stain they give more of the idea of cells filled with clear mucus. The lumen of the appendix is filled with broken-off glands. Only at the proximal end is there any normal structure of the glands.

The question comes up as to whether this is a true tumor, and should be placed under the classification of adenocarcinoma, or whether it should be called a mucous degeneration or proliferation, and should be likened to a polyp in other portions of the intestinal tract. We see this same proliferation of mucus in carcinoma of the rectum and other portions of the large intestine, where the cell structure is almost entirely lost, and we have nothing but large quantities of mucus with only occasional gland structures persisting.

The second case is one of what under ordinary conditions would be looked upon as a rather common tumor—a fibrosarcoma, and the interesting point here is as to whether it presents the histological evidence of malignancy. It is a type of tumor one sees often in the skin and subcutaneous tissues of various portions of the body, and we are often puzzled as to whether it should be called a fibroma, or fibrosarcoma, or a spindle cell sarcoma. I have no lantern slides of this case, but it has the ordinary appearance of a cellular fibroblastic tumor, the cells arranged in bundles, interlacing, and uniform in size. It is a well-encapsulated tumor; there is some ulceration on the surface.

As to the clinical history of the case, the patient was a woman of twenty-five, who at the age of nine years noticed a small lump on the back. This increased somewhat for a number of years until 1917 it reached the size of a walnut. The skin over it was normal. Five years ago she had an operation at Mount Sinai Hospital for the removal of the tumor. It recurred three years later, was then the size of a cherry, situated to the left of the original incision. She was treated for a period of three years with radium at the Radium Institute, for one year by radium alone with the removal of the tumor, and then treatment again with radium. During the last year the tumor was removed twice. At the Skin and Cancer Hospital we did the fifth removal with recurrence. This illustrates the recurrence of those tumors which have histologically the appearance of benign tumors.

The third slide which I have to show is one from a case of curettings in which from the histological appearance we made a diagnosis of adenocarcinoma or malignant adenoma of the uterus. The woman was fifty, with a history of some irregular bleeding between the menstrual periods, and with a small polyp at the cervix. The operation was for removal of the polyp. The hemorrhage was thought to be due to the presence of the polyp. It was small, and was not kept separate from the other curettings during the operation. In this case the picture seems to me sufficiently different from the normal

endometrium in any of the various stages of the menstrual cycle to justify a diagnosis of a malignant condition.

Discussion:

DR. WOOD: I think the appendix is a very interesting specimen, but we never shall know whether it is a carcinoma unless the patient develops a recurrence. It is a type of neoplasm rarely seen in the appendix. The mucocèles are often extremely difficult to diagnose, because they dissociate the muscle fibers and the cells grow out between the fibers of the coats, giving the appearance of true invasion, such as we see in malignant tumors of the gut. That has not occurred in the growth under discussion. But I have seen specimens of the mucocèle type in which it is perfectly impossible to say if it was a gelatinous carcinoma of the type frequent in other portions of the gastro-intestinal tract. I am inclined to think from the invasion of the muscularis, and from the general morphology of the cells seen in carcinoma of the rectum, that we are dealing with a true beginning carcinoma of the appendix. It is obviously entirely different from the well-known carcinoid growths, about which there is so much discussion.

The sarcoma illustrates a very important point. We pathologists are constantly being handed specimens by a surgeon and asked to make a prognosis. It is a very dangerous procedure to make a prognosis. It is certainly possible to do so for instance in a neurofibroma which is almost always called malignant by the average pathologist who has not had much experience. I often see such specimens where a diagnosis of sarcoma has been made on cellular neurofibromatous nodules which have been widely removed. This tumor at its present stage of course is a sarcoma. You see occasional mitotic figures, and the irregularity of the nuclei which suggest the diagnosis of sarcoma. I have seen such specimens where at the initial incision no such diagnosis could be made. The nuclei were all regular in distribution, size, and shape, the amount of interstitial tissue very large; there were no mitoses, and not the slightest evidence of anything malignant. After one recurrence they become more cellular, and after four or five they become still more cellular. I have seen the so-called myxomata go through years of recurrence, each return getting more and more cellular, until the final stage was a general invasion of the body with a highly metastasizing tumor. Of course this tumor should have been widely excised at the initial operation on the patient, and it thoroughly illustrates the point that there is only one time to do surgery, and that is the first time. There is still too much poor surgery being done at the best hospitals and by the best men in the City of New York. They do not realize that there is only one chance in cancer surgery. I think using radium and x -ray on these tumors, while interesting as a matter of research, does not cure them. They are highly resistant to these agents. A guinea-pig fibro-sarcoma now growing at the Crocker Laboratory will resist nine or ten erythema doses, which means if the patient had that tumor the necessary dose of x -ray would kill the patient. Even by burying radium needles, sloughs may be produced in these tumors, and a portion of them destroyed, but we cannot affect the whole tumor by radiation, in which case radiation is no better than cutting the tumor out.

The last specimen of Dr. Jessup's, it seems to me, is a very early adenocarcinoma of the uterus, and an interesting specimen from that point of view.

A CASE OF PRIMARY TRICUSPID ENDOCARDITIS

CLARENCE DE LA CHAPELLE, M.D.

Among 8,373 autopsies at Bellevue Hospital, this is the fifth case of endocarditis confined to the tricuspid valve, and hence seems sufficiently rare to be worth reporting. The four previous cases were reported by Dr. St. George, together with a fifth case which he had encountered in a series of 429 autopsies in the American Army.

The patient, a man, aged fifty-five, was admitted to Bellevue Hospital on May 17, 1922, complaining of pain in the right chest, cough, and expectoration of bloody sputum. He gave a history of having been drinking heavily for several weeks and of having been exposed to dampness while at work. There was no history of rheumatic fever or tonsillitis. He had had malaria twenty-five years ago.

On admission the temperature was 101.8° F., pulse 104, respirations 24. There was dulness in the right base and broncho-vesicular breathing with crepitant râles and increased voice sounds in the right axilla. The diagnosis of lobar pneumonia was made. The left border of the heart percussed 11 cm. from the mid-sternal line in the fifth intercostal space. No definite murmurs were heard but the heart sounds were distant; rate 78, rhythm regular.

On May 27 the patient had a chill lasting thirty minutes; the temperature was 98.8° F. at this time. Four days later dulness was elicited over the right upper and middle lobe with bronchial breathing and bronchophony. Diagnosis: Unresolved pneumonia.

On June 15 the patient had another severe chill of malarial type according to the note on the chart. No malarial parasites were found in the blood smears. The blood pressure was 102 systolic; 68 diastolic. The urine showed a trace of albumen and a few white blood cells. An x-ray, taken about this time, showed marked fibrosis of the right upper lobe with retraction of the trachea to the right, but no other evidence of infiltration or consolidation was seen.

A week later the heart sounds were clearly audible to the right of the sternum where dulness on percussion extended out 3.5 cm. from the right margin of the sternum. Diagnosis: Fibrous retraction of the heart. The sputum was blood tinged. A blood culture taken on this date was reported as sterile after three days' incubation.

On July 6 the patient had a severe chill lasting one half hour, vomiting during and after the chill. He complained of severe pain in the left side of

the chest. The temperature was 103° F.; pulse 88. Dulness was elicited over the left upper lobe anteriorly and posteriorly. Bronchial breathing and bronchophony were heard over the same area. The white blood count was 40,800; polymorphonuclears 89 per cent.; lymphocytes 11 per cent. Diagnosis: Lobar pneumonia (left upper lobe).

The following day the temperature was again normal. About three weeks later the patient had several distinct chills over a period of four hours, after which he felt weak. The spleen was palpable. The heart sounds were of poor quality, rate 100; sinus rhythm; the blood pressure was 98 systolic, 70 diastolic. Quinine was given, the signs and symptoms being suspicious of a malarial flare-up.

On August 8 another blood culture was reported as being sterile. The urine showed a few white blood cells and a few granular casts. An x-ray picture taken about this time showed partial consolidation in the basal and peripheral portions of the right upper lobe. The remainder of the lobe showed evidence of marked interstitial changes with a moderate degree of bronchiectasia. There were also interstitial changes in the right lower lobe. Moderate dilatation of the aorta was noted. X-ray diagnosis: Interstitial pneumonia, multiple abscesses, fibrosis, aortitis.

On August 11 the patient left the hospital against the advice of the physicians. In a little over two weeks he was readmitted, complaining of bloody and purulent sputum; pain in the left shoulder; chills, fever, sweats; weakness and loss of weight. The temperature was 101° F.; pulse 110, respirations 28. Examination showed a man who appeared chronically ill, with pallid and drawn face, perspiring profusely. The sputum was described as purulent and tinged with blood. Percussion gave marked dulness over the right upper chest posteriorly with broncho-vesicular breathing and amphoric breath and voice sounds over the apex. Tactile fremitus was increased. Over the right upper chest anteriorly the percussion note was suggestive of cracked-pot resonance, with amphoric voice and whisper. Moist râles were heard in the third right interspace. Percussion at this point was painful. Breath sounds were increased over the left chest.

The left border of the heart percussed 6 cm. from the mid-line in the sixth interspace. The heart sounds were muffled, of poor quality, and sinus arrhythmia was present. The rate was 84; no definite murmurs were localized; sounds at base were distant. The spleen was palpable. The liver margin palpated 7 cm. below the ensiform. The left shoulder joint was enlarged, painful, and felt hot. The white blood count was 11,000 with 74 per cent. polymorphonuclears and 21 per cent. lymphocytes. The red blood count showed a slight anemia—3,800,000 cells with 75 per cent. hemoglobin. Diagnosis: Abscess of the right upper lobe with cavitation (post-pneumonic); septic arthritis of the left shoulder joint; retraction of the heart to the right.

About a month later an x-ray showed a moderate amount of fibrosis and bronchiectatic cavity formation of almost the entire right lung. There was evidence of resolving pneumonia of the central portion of the left lower lobe with interstitial changes in the remainder of the lobe. There was slight retraction of the heart and of the trachea to the right due to fibrosis in the right

lung. X-ray diagnosis: Bronchiectasia, right lung; resolving broncho-pneumonia, left lower lobe.

FIG. 1.

On September 28 another x-ray report stated that there was a partial pneumo-thorax of the right pleural cavity (an artificial pneumo-thorax having been performed in the interval) producing about ten per cent. collapse of the lower lobe. There were several adhesions between the visceral and parietal pleuræ and also diaphragmatic adhesions to the right lower lobe.

On October 4 a large hemorrhagic rash was seen over the left thigh, hip and back. A week later a blood culture, taken on the 8th, was positive for *Streptococcus viridans*.

On October 13 the patient felt weak and asked continually for another artificial pneumo-thorax. The pulse was small and weak; rate 96. The day before his death the respirations were 30, pulse small and thready, rate 120. The patient died on October 16, five months after his first admission.

Autopsy was performed two hours post-mortem. The precordial area

was small, the left lung overlapping it for a considerable distance. The subepicardial fat over the right ventricle was yellowish brown in color, of jelly-like consistency and serous fluid escaped on sectioning it. The right auricle was distended. On opening it a large, pinkish-green, polypoid mass, measuring about $2 \times 4 \times 6$ cm., was present, bulging into the auricular cavity. The right atrio-ventricular orifice was practically occluded. The vegetation was covered here and there with patches of clotted blood, but otherwise it was quite smooth. The mass was situated on the anterior cusp of the tricuspid valve and was firmly adherent to it. The three cusps, which were greenish in color, were so welded together and thickened that they were practically indistinguishable one from the other. The chordæ tendinæ were thickened and shortened. The apex of the left ventricle presented a small clot of blood which was adherent to the columnæ carneæ, and on removal left a roughened muscular surface. The remaining heart valves were normal. The coronaries showed no lesion. The aorta was normal.

Anatomical diagnosis: Primary polypoid thrombo-endocarditis of the tricuspid valve; obliterative pleuritis (right upper lobe); chronic interstitial pneumonia (right upper lobe); chronic caseous tuberculosis (localized, right upper lobe); compression atelectasis (right lower lobe); lobular pneumonia (left lung); left hydrothorax; chronic septic splenitis; petechial hemorrhages in the mesentery, omentum and kidneys; acute parenchymatous nephritis; subcutaneous hemorrhages; subacute bacterial endocarditis.

Bacteriological examination: Showed small, gram-positive streptococci in pairs and short chains in a smear made by crushing a piece of vegetation from the tricuspid valve.

Microscopic examination: Heart—1. Section of the vegetation showed that it was composed of hyaline structureless material and fibrin. Gram-Weigert stain showed the periphery of the vegetation to be filled with innumerable, small, gram-positive streptococci, which appeared singly, in pairs and in chains. The interior portion of the thrombus showed no organisms.

2. Section of apex of right ventricular wall showed a large subendothelial collection of leucocytes, which infiltrated between the scanty muscle fibers, most of which had been replaced by fibrous tissue. This exudate was made up of polymorphonuclear leucocytes, lymphocytes, endothelial and plasma cells. The muscle at a distance from this lesion appeared fairly normal. Gram-Weigert stain of a section taken from the same portion of the heart demonstrated in the affected area organisms identical with those found in the vegetation.

3. Sections of the kidney showed that the lining membrane of the capsules of many of the glomeruli was proliferated, swollen and in some cases desquamated. Other glomeruli showed fibrin thrombi in the capillary tufts. In still others the capillary tufts were intensely congested and leucocytes were seen in the capsular space and beneath the epithelial lining of the capsule. The tubules presented no marked changes except that some of them contained leucocytes and red cells. The vessels of the organs had moderately thickened walls.

At Guy's Hospital over a space of forty-six years (1860–1906), during which time twenty-one thousand autopsies were

performed, thirty-five cases of infective endocarditis of the tricuspid valve were encountered. Of these, twelve showed involvement of the tricuspid only. These figures are proportionate to those of Bellevue Hospital, namely about one case of primary tricuspid endocarditis to every 1,750 autopsies. In the Gulstonian Lectures of 1885, Osler analyzed 209 cases of endocarditis and found the tricuspid valve involved alone in only five instances. In thirty-four cases of so-called subacute bacterial endocarditis studied by Libman which came to autopsy, not one instance of tricuspid involvement was noted.

The case just presented was a male fifty-five years of age. The five cases reported by St. George ranged from twelve to sixty-eight years of age; males predominated. The majority of cases reported in the Guy's Hospital statistics were between the ages of ten and forty years; the number of male and female cases was about equal. Infants and children seem to be almost exempt from endocarditis other than that due to acute rheumatic fever and chorea. Congenital (fetal) endocarditis on the other hand is not an infrequent finding and is almost always confined to the right side of the heart. In 237 cases of congenital endocarditis, Rauchfuss found right-sided lesions in 192. According to Osler, this relative frequency of endocarditis on the right side is probably due to greater tension which has to be borne during fetal life in contradistinction to the lessened strain put upon the tricuspid valves in adult life.

As regards the causative agents in these cases of tricuspid endocarditis, the findings are variable. In two of the cases recorded by St. George, blood cultures were taken, one showing the presence of *Staphylococcus aureus*, the other *Pneumococcus*. Cultures were made from a lung infarct and a heart valve in a third case and both showed *Streptococcus hemolyticus* in pure culture. In the case presented here the third blood culture was positive for *Streptococcus viridans* of Schottmueller, as was also the smear from the vegetation.

To the above-mentioned organisms, namely the *Staphylococcus*, *Pneumococcus* and the two varieties of *Streptococcus*, may be

added the *Gonococcus* and the Influenza bacillus, as being important causes of malignant endocarditis. The term "malignant" as first employed by Osler in describing cases of acute endocarditis is clinical rather than anatomical, and refers to cases with severe constitutional disturbances and extensive valve lesions, whether ulcerative or vegetative lesions. Pneumonia heads the list of all diseases complicated by severe endocarditis (Osler). G. W. Norris states that lesions of the right heart are more common in this form than in other varieties of endocarditis. In 141 cases of endocarditis in pneumonia, Preble encountered twelve, or 8.5 per cent., which involved the tricuspid valve alone.

The case presented to-night illustrates the type of endocarditis produced by the *Streptococcus viridans* of Schottmueller or the endocarditis coccus of Libman. The disease is comparatively slow in its progress; of about five months' duration in our case and from four months to one year or even one and one half years in forty-five cases studied by Libman. As MacCallum states, the heart valves are subject to remissions or periods of partial healing, but the disease nevertheless goes on to the death of the patient.

Vegetations due to the *Streptococcus* are apt to be large and to grow rapidly. Occasionally they are so massive, as typified in the case here presented, as practically to occlude the valvular orifice. It is stated (Norris, G. W.) that vegetations of considerable size are more apt to produce insufficiency than stenosis. In the majority of the Guy's Hospital cases of tricuspid endocarditis the valves were incompetent, yet in only five cases was a systolic tricuspid murmur noted; one case gave a diastolic murmur. No definite murmurs were noted in the case here presented.

The general symptoms of tricuspid endocarditis are the same as those present in any case of malignant or subacute bacterial endocarditis, namely fever, with or without chills, progressive weakness, enlarged spleen, hematuria, petechiæ and painful cutaneous nodules.

Since the diagnosis of tricuspid endocarditis is usually dependent upon the presence of insufficiency or stenosis of the valve,

reference is made to the extensive discussion of "Tricuspid Stenosis and Tricuspid Insufficiency," by Young and Cotter, and to St. George's paper on "Malignant Tricuspid Endocarditis" (see References).

The striking features about the case presented were:

1. Its likeness to malaria as shown by the chills, fevers and sweats.
2. The lung changes which accompanied the heart lesion.
3. The absence of any definite cardiac symptoms, dyspnoea or edema never having been complained of.
4. The similarity of the pathological lesion in the kidneys to that found in subacute bacterial endocarditis as described by Baehr before this Society in 1911.
5. The massive vegetation on the tricuspid valve with no involvement of any of the other heart valves.

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Discussion:

DR. ST. GEORGE: The clinicians' diagnosis is not always confirmed at autopsy. The case I had in the Army was that of a negro who was seen a great number of times on the ward, as he ran a chronic course. All the attention was focussed on the lung condition; he had, it was thought, an influenzal pneumonia with empyema; he was operated on and nothing was found. At autopsy, however, the endocarditis was encountered. The diagnosis of the condition is, of course, very difficult. In this case there were no heart murmurs encountered. The above patient and the records in the Bellevue cases differ from the case presented tonight in that all had heart murmurs, only they were not properly interpreted. I think that this case opens the question as to whether the lung condition was primary and the endocarditis merely a

terminal infection, or whether the endocarditis produced the lung symptoms, as is generally thought to be the case. In this particular instance there was a good deal of fibrosis through the lung, and I doubt whether one could justifiably attribute the lung symptoms to the heart. It is quite possible that he had pneumonia and that the heart affection was simply a terminal event.

HETEROGENEOUS TISSUES IN FEMALE SEXUAL ORGANS

EMIL SCHWARZ, M.D.

The few cases to be demonstrated to-night require for their explanation certain embryological data. The gross specimen is an intra-mural tumor of the corpus uteri weighing twelve and a half pounds, well defined against the myometrium. It is composed almost exclusively of a yellow, very soft tissue with occasional islands of a greyish firm tissue, which also prevails in the periphery and fuses with the yellow structures. The growth is plainly a lipo-myoma, which on microscopical examination shows the typical appearance of this rather infrequent tumor. Up to 1908 there were seventeen cases reported, and one recent case in 1920 was described by Williamson and Brockman in the *Proceedings of the Royal Society of Medicine*, London, which had been removed sixty years before by Sir James Paget. The lipoblasts described by several authors were present in the reticulum, as well as in the smooth muscle islands. Besides that numerous mononuclear eosinophilic cells and large cells with fine delta granulations, staining well with Dahlia, can be seen in sections. In the sixth edition of Killiker's Histology there is a reference to these cells which according to the author are present in the tunica dartos of the testicle, and which he assumes to be predecessors of the lipoblasts. This fast growing tumor, which is entirely benign, seems to present all the stages of the formation of fat cells. In order to explain this and some of the following cases, I am showing on the screen a 1.38 mm. embryo of Pfannenstiel-Kroemer, and a 2.8 mm. embryo of my collection. The differentiation taking place in the nephrogenic cord between these

two embryos indicates that mesenchymal persistent tumors, as well as "faulty mixtures and aberrations," must occur after the first shown embryo and before the second is developed.

FIG. 1.

I am also demonstrating a cyst 2.5 cm. in diameter, developing laterally of the introitus vaginæ at the level of the hymen. The

cyst is lined with one or two layers of a high columnar ciliated epithelium. The site of the epithelial lining and the exclusion of other possibilities lead to the assumption of a cyst of Gartner's duct.

Microscopically entirely different, but histogenetically identical, is another specimen showing numerous glandular lumina which are located in the stroma of the cervix uteri near the attachment of the broad ligament. These glands are lined with a low cuboidal epithelium easily distinguished from cervical glands. Although resembling epoophoron tubules they are apparently cross sections of a branched ampulla of Gartner's duct, since remnants of Wolffian body cannot occur below the second crossing of the latter and the tubal portion of Mueller's duct.

A section which I am at a loss to explain shows on the convexity of an otherwise normal, perfectly free ovary a small growth arising from a groove in the albuginea of the ovary. The cytogenic stroma of this funnel-shaped growth, which measured 1.5 mm. in diameter, contained numerous glands of the corpus type, and sent a short processus into the ovarian stroma (Fig. 1).

PURE CULTURE OF B. INFLUENZÆ FROM PELVIC ABSCESS

PAUL C. MORTON, M.D., AND L. W. FAMULENER, M.D.

(*From the Pathological Laboratory of St. Luke's Hospital, F. C. Wood, Director*)

The influenza bacillus of Pfeiffer is commonly associated with diseases of the respiratory system, including the nasal passages and the accessory sinuses. It may be the specific etiologic factor in some of these conditions, while in others only a secondary invader. Its primary importance as the cause of epidemic influenza, first postulated by Pfeiffer, has been questioned in the last few years by various investigators. Some would relegate this organism to a secondary rôle in the disease. Regardless of whether or not it is the cause of true influenza, it is frequently

associated with other acute infectious diseases such as measles, scarlet fever, whooping cough, chickenpox, and diphtheria, where it occasionally may be present in the blood stream. The respiratory system harbours it in the more chronic conditions of the lungs, as pulmonary tuberculosis, bronchitis, bronchiectatic cavities, while empyema exudates may contain the organism. It has been recovered from the central nervous system in cases of cerebrospinal meningitis and more rarely brain abscess, while the special sense organs show involvement as in otitis media and possible extension into the mastoid cells. Acute contagious conjunctivitis ("pink eye") falls in this class, and may be the result of the Koch-Weeks bacillus, which some competent bacteriologists consider identical with the influenza bacillus. In the gastrointestinal tract it has been recovered repeatedly from the mouth, tonsils, and throat. It is often found in the accessory nasal sinuses. Further, an acute and chronic gall-bladder infection may be due to this bacillus, and appendicitis and peritonitis may develop. Frequently the influenza bacillus in these conditions is associated with other pus-forming organisms.

Septicemia with recovery of the organism was observed shortly after the discovery of the bacillus, and endocarditis with vegetations in which influenza-like organisms have been found demonstrates its presence in the cardio-vascular system. The genito-urinary tract is not exempt, for cases of cystitis have shown the influenza bacillus to be present in culture.

From this brief survey one can see that the organism has the ability to invade and establish itself, either primarily or secondarily, with the ancillary organisms—the pneumococcus and the streptococcus—in practically all regions of the body. It would appear that even in inter-epidemic periods this organism is always present to a certain extent among individuals as carriers in thickly populated areas and cities, and may give rise to sporadic outbreaks, or isolated cases of infection. Probably the true nature of some of these infections is not recognized clinically, or laboratory examinations have not been undertaken as an aid to diagnosis. Recently, the authors had an opportunity to study

such a case, through the courtesy and helpful cooperation of Dr. E. D. Truesdell, Assistant Attending Surgeon of St. Luke's Hospital, to whom we are further indebted for clinical and operative notes.

In a brief survey of the literature, we have found no report of a similar condition, therefore we take the occasion to present to this Society the history of the case with the laboratory findings:

Case No. 162,734. Admitted to St. Luke's Hospital, November 2, 1922. The patient was a young woman, aged twenty-eight years, and of American nationality.

Marital history shows her to have been married at the age of twenty. There had been one pregnancy, the child a boy now seven years of age. She has been a widow for three years.

Past history discloses the following facts: She suffered from the usual infectious diseases of childhood. Three years ago, during the influenza epidemic, she had an illness characterized by chills, fever and cough which kept her in bed for a week. Her physician pronounced it a "heavy cold." Gastro-intestinal history states that she is subject to constipation of the bowels and has never had attacks of diarrhoea until one or two days before admission to the hospital. At this time there were seven movements daily. There have been no recurrent colds or attacks of bronchitis, although she suffers from the usual and occasional "cold in the head." She gives no history suggestive of chronic sinus involvement, and there has never been an acute or chronic vaginal discharge.

Present illness: The onset occurred one week before admission, the patient being confined to bed with pain in the lower half of the abdomen and in the back, cramp-like in character, of half hour's duration, and reappearing at three- to four-hour intervals. As in the other attacks she felt feverish. There was no nausea or vomiting at any time during the illness. The bowels were constipated except for the moderate diarrhoea just before coming to the hospital which was mentioned above. The patient had had two similar attacks of less severity and short duration (twenty-four hours) in the preceding March and August. She was confined to bed one day in each instance.

On admission the patient had a temperature by mouth of 99.8° F., which rose to 100.4° on the following day.

Physical examination: The patient appeared well nourished, with good color, showing no evidence of acute sickness. There was no rigidity of the abdomen and no masses were felt. Upon deep pressure there was moderate tenderness in each groin. The uterus could not be felt anteriorly in pelvic examination, but in the posterior fornix a mass of moderate size was found which was moderately tender. A pre-operative diagnosis was made of retroflexed and retroverted uterus, chronic salpingitis with pelvic adhesions.

Operation: Upon opening the abdomen the body of the uterus was found to be in the normal position. The pelvis was occupied by a mass composed of adherent sigmoid and small bowel. Upon separation of the adhesions yel-

lowish-green, odorless, thin pus was liberated. Culture material was taken upon sterile surgical swabs and sent to the Bacteriological Laboratory for examination. Both tubes were found to be red and congested in appearance, but not thickened; the outer extremities were not occluded. The ovaries appeared normal. The adhesions were separated sufficiently for evacuation of the pus and the insertion of a drain. Attention was then directed toward the appendix, where no adhesions were observed in the right iliac fossa, either of the omentum or small bowel, to or about the cecum. Upon elevation of the cecum the appendix was found plastered to the posterior surface of that structure and somewhat buried in it, and adherent to the mesenteric attachments of that region. Upon attempting to free the appendix, about a dram of pus similar to that found in the pelvis was liberated. The appendix was red, slightly swollen, but without perforation, gangrene, or appearance to explain the small retrocecal appendix abscess. The appendix was removed and a drain placed in the lower angle of the abdominal wound reaching to the bottom of the pelvis and the remainder of the wound closed.

Post-operative diagnosis: Pelvic abscess, retrocecal abscess about appendix; secondary subacute appendicitis.

Laboratory examinations: A full blood count made on the day following admission showed red blood cells 3,800,000, hemoglobin 84 per cent.; white blood cells 14,000; polynuclear leucocytes 88; lymphocytes 12.

The Wassermann reaction was negative.

Bacteriological examination: Cultures were made of pus upon dextrose agar slant, dextrose broth, and human blood agar plate. No growth developed after the usual incubation on either the dextrose agar slant or the broth, but upon the blood agar plate small colonies appeared, which were found to be composed of small Gram-negative bacillary forms morphologically characteristic of the influenza bacillus. Fishings made from these colonies transplanted to dextrose agar slants and broth failed to develop a growth after several days' incubation. On the other hand, similar transplants upon five per cent. human blood agar slants showed typical growths of the influenza organism on incubation. Transplants from these cultures again failed to develop growth when transplanted to dextrose broth or carried through a series of transplants to dextrose agar slants. The organism was reported as *B. influenzae* in pure culture.

Pathological examination of appendix (Dr. L. C. Knox).

Diagnosis: Subacute appendicitis.

Macroscopic examination: Specimen consists of an appendix 4 cm. in length. It has been opened in the operating room. The peritoneal covering has lost its luster, but is not markedly injected. The mucosa appears thickened and there are small hemorrhages in the submucosa, but the markings are fairly distinct throughout.

Microscopic examination: Section of the appendix shows a subacute infectious process which has involved all the coats, but which shows evidence of considerable healing. There is no necrosis. The exudate has been largely absorbed, although there is still increased vascularity throughout, edema, and productive areas in the mucosa and submucosa. Both of these coats contain

fresh hemorrhages and their capillaries contain unusual numbers of polynuclear cells. There are collections of round cells in the perivascular spaces of the muscle coats and in the subserous reticular tissue. Since all the coats are affected, the process appears to have originated within the appendix, rather than to have been an extension from the pelvic inflammation.

Subsequent course: The convalescence was uneventful, the patient having left the hospital within two weeks with a small sinus and slight discharge.

From the bacteriological standpoint this case is of interest owing to the unusual finding of *B. influenzae* in pure culture of pus from a pelvic abscess. The original source of the infection and the route of invasion of the pelvis are matters subject only to speculation, since none of the possible explanations can be proved. No primary focus of infection in the patient, such as a pulmonary condition (recent influenza, bronchitis, etc.) or accessory nasal sinus involvement, could be found. There were no gastrointestinal disturbances, other than the three attacks during the last seven to eight months which might indicate a mild appendix involvement. Unfortunately the appendix after removal at operation was not sent to the Bacteriological Laboratory for cultural examinations; therefore the question of whether it showed the presence of *B. influenzae* cannot be answered. Presuming that the influenza bacillus was present and had broken through the wall of the appendix, a mixed infection with intestinal types of organisms might have been expected. Another possible route of invasion to the peritoneum might occur through the vagina, uterus and tubes, although the history offered no evidence of any infection of the genito-urinary tract. Among other sources of infection the blood stream or the lymphatic system might possibly carry the organism from a focus such as the tonsils, or from the urinary tract, and deposit it in the region where found. The question whether the infection in the pelvis was primary or secondary to some other focus in the body still remains open. If the latter, perhaps the appendix should be given first consideration.

A CASE OF SULPHEMOGLOBINEMIA

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In 1910 Clarke and Curtis¹ described the first case of sulphemoglobinemia recognized in America, but no other instances of the affection were reported in this country till 1921. Mason and Conroy² in that year published a typical case, stating that it was the thirteenth so far put on record. The present case of sulphemoglobinemia was seen and studied by the present writers in 1916, making it the fourteenth example of the condition to be reported, and the second of the three so far found in this country.

The patient, who was first seen on February 28, 1916, was a young man whose appearance was remarkable in that his lips and ears were distinctly blue and his features of a livid pallor. He stated that for the past three weeks he had suffered from vertigo and fainting attacks, a severe attack occurring on the preceding day. His employment was in a chemical factory in which he was engaged in the production of a photographic developer containing para-amido-phenol, made by the electrolysis of nitrobenzene in a concentrated sulphuric acid solution, lead electrodes being used. The skin of his hands was thickened, rough and fissured. No drugs had been taken except some tablets of sulphur and cream of tartar. He had been told by a physician that he was suffering from lead poisoning.

Examination of the heart and lungs revealed no abnormalities and the routine examination of the urine was negative. Further tests proved the absence of phenol, urobilin, urobilinogen, or blood pigments. The blood examination showed 5,200,000 red cells, hemoglobin 80 per cent., 10,000 leucocytes, with polynuclears 76 per cent., lymphocytes 22 per cent.; and eosinophiles 2 per cent. The stained smear showed no basophilic stippling of the red cells, nor anything else of note. The Wassermann reaction was negative.

In the absence of any pulmonary or cardiac condition to account for the cyanosis the possibility of poisoning by some of the agents with which his occupation brought him in contact suggested itself and the blood was examined with the spectroscope. An absorption band was visible between the C and D lines, in about the position of the characteristic band of methemoglobin, but as one of the authors had seen and studied Clarke's patient with sulphemoglobinemia, who for a time was under investigation at St. Luke's Hospital, it seemed possible that this was an instance of the same condition, and further tests were performed. Comparison of the band in the patient's blood with the spectrum of artificially prepared methemoglobin showed that it was further to the right than the band of the latter. The addition of ammonium sulphide

to a solution of methemoglobin causes the band of this substance to disappear, while the spectrum of sulphhemoglobin is unaffected by this treatment. The test confirmed the identity of the pigment in the patient's blood, and in order to complete the demonstration synthetic sulphhemoglobin was prepared, and its spectrum was found to be absolutely coincident with that obtained from the patient's blood. In making these observations a comparison spectroscope was used, making it possible to note with absolute accuracy the slightest differences in the position of the absorption bands.

Tests made on the serum showed that it contained no sulphhemoglobin, but that a reducing substance was present. Tests for nitrites were negative in the blood, the serum, and the urine, but positive in the saliva.

Two weeks later the patient's appearance had improved and his symptoms had almost entirely disappeared, but the sulphhemoglobin was still present in marked amount.

On March 22 he reported that he had been able to go back to work, and though sulphhemoglobin was still easily demonstrable it was less in amount. During the following weeks he was seen repeatedly and the sulphhemoglobin did not entirely disappear from the blood till June 26, though the serum still showed a slight reducing action.

Wallis³ ascribed etiologic significance to the presence of a Gram-negative, cocco-bacillary organism with reducing properties which he found in the mouths of five English patients suffering from sulphhemoglobinemia, and an attempt was made to confirm this observation in our case. Cultures made following the methods used by Wallis were negative as far as any forms corresponding to the "nitroso-bacillus" were concerned, and blood cultures made under both aerobic and anaerobic conditions were also negative.

Cyanosis may be produced by overdoses of various drugs, especially acetanilid, phenacetin, trional, sulphonal, potassium chlorate, nitrites and nitrobenzol; not through cardiac depression, as often believed, but through the formation of methemoglobin. In a few reported instances methemoglobinemia has been observed though no external cause for its production could be discovered and to this condition the name of enterogenous or idiopathic cyanosis has been applied. These patients all suffered from severe diarrhea, were markedly cyanosed, and as nitrites were found in the blood by von der Bergh and Gutterink,⁴ it has been believed that the absorption of nitrites from the intestine was responsible for the production of the altered blood pigment. In 1906 von der

Bergh reported four other cases, however, equally of unknown etiology and resembling the former group except that the patients were all constipated. Careful study of the blood with the spectroscope showed that the spectrum given was not that of methemoglobin but that of sulphhemoglobin. It was also found that while temporary disappearance of the methemoglobinemia followed putting a patient on an exclusive milk diet for forty-eight hours, no change occurred under these conditions in the sulphhemoglobinemia cases. Several other authors have described similar cases, three of which have been recognized in this country, the first discovered by T. Wood Clarke in 1910 and reported by him after study in St. Luke's Hospital, the present case observed in 1916, and that of Mason and Conroy seen in 1921. The latter case and our own are the only instances in which the patients have been adult males, all the others being females except one of von der Bergh's, who was a young boy suffering from a congenital stricture of the rectum and a rectovesical fistula.

From the studies of Clarke and Hurlley⁶ it appears that the presence of reducing substances greatly facilitates the production of sulphhemoglobin from even minute traces of sulphuretted hydrogen. Wallis believed he had found the source of such a reducing substance, needed to aid in the formation of sulphhemoglobin from the sulphuretted hydrogen of the intestine, in the isolation of a "nitroso-bacillus" in the saliva. This could not be found in our case, and similar failures are reported by Long and Spriggs, and also by Mason and Conroy.

The manner in which the formation of the abnormal blood pigment is brought about is still unknown, but it appears that two factors must gain access to the blood, sulphuretted hydrogen and a reducing substance, and in most cases it is probable that the former originates in the bowel. In our patient's case several significant features are to be noted. Unlike most of the reported patients he had not been a sufferer from constipation, and his blood affection developed in connection with two special circumstances. One was that he had been taking a preparation containing sulphur, and the other that the sulphhemoglobinemia de-

veloped rather quickly at a time when he was showing the evidences of nitrobenzol poisoning in the condition of his fissured, scaly and itching hands. After he had stopped taking the sulphur, and had been protected from the action of the nitrobenzol by absence from his occupation and later by wearing rubber gloves when at work, the sulphhemoglobinemia disappeared, a behavior very different from what has generally been noted, as in most cases the condition has proved very intractable to treatment. It is suggested that in our case the sulphhemoglobinemia was of a different type from that heretofore described, and that in this case the combination of the two factors of the ingestion of sulphur, and the absorption of nitrobenzol brought about the formation of the abnormal blood pigment.

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CONGENITAL ABSENCE OF GALL BLADDER

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Fifty-seven years ago Dr. Henry B. Sands showed before this Society a rather infrequent malformation consisting in the absence of the gall bladder and therefore the demonstration of a similar specimen may not be without interest, especially as none have been shown here in this interval.

The French anatomists have given more attention to the subject than others, and have said that such an omission is not really infrequent but their literature reveals not more than a score

of cases. In the *Transactions of the Philosophical Society of London* for the year 1701 L'Emery is said by Eschner to have described the liver and hepatic ducts of an infant without a trace of a gall bladder in the specimen. References are made in the literature to about forty other instances of this defect, although it is possible that a few of these are described twice, several of the specimens in the anatomical museums of the London hospitals having been referred to a number of times. Many of the references cannot be verified. Kehr, summarizing the subject, mentions six cases in infants with other malformation and thirteen cases in adults, two associated with malformation of the liver.

Abstracts of the available cases are as follows:

1. Huber, 1744. Author showed liver of woman 60 years of age with no gall bladder. Hepatic ducts were much dilated.

2. Sir E. Home, 1813. Infant a few months of age. Appeared fairly healthy at birth, took feedings readily but became emaciated, skin darkened in color, and all subcutaneous fat disappeared. At autopsy no trace of gall bladder was found.

3. Wilson (cited by Canton). Described a liver with a shallow groove in its substance replacing the gall bladder. The hepatic ducts were normal, the common duct was dilated, and its mucosa furrowed, resembling that of the gall bladder.

4. Canton, 1847. The author autopsied the body of a woman 65 years of age who had died of cerebral hemorrhage, and found the liver two thirds the normal size, the gall bladder missing, the hepatic ducts normal in position and calibre; but the common duct was twice normal size and its mucosa was rough and furrowed. The cystic artery was absent.

5. Thomas, 1848. An infant five months of age had been jaundiced from its second day, had vomited almost continuously; the stools were white, the extremities edematous, and the abdomen contained bile-tinged fluid. There was no gall bladder and no extra-hepatic ducts affording any drainage whatever.

6. Harle, 1856. Brief mention was made of a liver found at autopsy, colored dark green and with no trace of a gall bladder and no cystic duct.

7. Simpson, 1861. The writer attended a new-born child suffering from diffuse lesions of the skin at first thought to be sclerema but these later suppurated and were found to be infectious. The infant vomited continuously and died at the age of four weeks of peritonitis. There was no gall bladder and no fossa in the liver but the other ducts were normal.

8. Patterson, 1864. At autopsy on the body of a man 35 years of age who died from asthma, the liver was found four times normal size, soft and fatty with no trace of a gall bladder.

9. Sands, 1865. The writer demonstrated before the New York Patho-

logical Society the liver of a male who had died of tuberculosis at the age of 20. There was no quadrate lobe, no fissure for the gall bladder, and the hepatic ducts were somewhat dilated.

10. Pozzi, 1872. This writer described a monster, not viable, with hernia of the diaphragm and several other gross anatomical defects, among them complete absence of the gall bladder and all extrahepatic ducts. The similar case of Porak is cited.

11. Lynch, 1875. This case also occurred in an infant, jaundiced since its second day and dying in the eleventh week. There were multiple hemorrhagic cutaneous lesions; the stools were white, and there was constant pain and tenderness in the epigastrium. The liver was found to be large, the hepatic ducts small and the gall bladder missing. All tissues were intensely jaundiced. The common duct was not dilated. The pancreas was apparently normal.

12. Rambault and Schachman, 1882. A liver was described without gall bladder but with normal hepatic ducts. The conditions occurred in a paretic and had apparently caused no symptoms.

13. Hochstetter, 1886. The liver of an infant who had died at the age of eight days was shown. The right lobe was very large, the quadrate lobe absent and the left small. The gall bladder was missing and the ductus choledochus, placed slightly further than usual to the left, entered the duodenum at a point higher than normal.

14. Eschner, 1894. Twelve cases of missing gall bladder were enumerated by this writer, but many of them he himself regarded as probably resulting from inflammatory processes and not a primary agenesis. The author's own case was found in the body of a child two years of age. Death was due to pneumonia. The liver, otherwise normal, possessed no gall bladder.

15. Kirmisson et Herbert, 1903. The case occurred in a phocomelus infant one month old who died of a pulmonary infection. The child had been jaundiced since its third day. The liver was hard, green, and had no gall bladder as well as no ducts connecting it with the intestinal tract.

16. Blakeway, 1912. At autopsy on the body of a newly born infant several defects were found—absence of the gall bladder, non-development of the corpus and cauda of the pancreas, and a blind sac at the end of the rectum, this cloacal pouch communicating with the prostatic urethra.

17. Torrence, 1920. This surgeon has been apparently the only one to record the complete absence of a gall bladder discovered in the course of a laparotomy. The patient was a male thirty-eight years of age, upon whom appendectomy had been performed. The common duct appeared normal.

Possibly the specimens mentioned by Mayo-Robson, Walton, Latham, and Thursfield are the same as those described elsewhere.

Interest in the subject centers in the fact that the omission represents a definite congenital defect with which is more than likely to be associated some other defect. Of the sixteen cases

regarding which the facts are at hand, other gross abnormalities have accompanied them in three instances and in four infants there have been no means of communication with the intestinal tract. Mayo-Robson has stated that life could exist for months in this extraordinary condition, referring perhaps to the case of Cnopf (cited by Kehr), who observed an infant with no ducts or gall bladder, but who survived for twenty-three weeks. It will be noted that in the case of Thomas the infant lived for five months, while the one observed by Kermisson and Herbert lived for one month. Jaundice and metabolic disturbances were clinically prominent features of each case, but death was directly due to infection.

Since ten of the cases are known to have died in infancy, it is probable that in these there were also other serious defects, anatomical or functional. If, on the other hand, the ducts are of normal calibre and distribution, the absence of the gall bladder from birth may cause even less disturbance of function than follows the surgical removal of the viscus.

The question of compensatory dilatation of the common duct after cholecystectomy is by no means settled, although the opinion prevails that such will occur unless infection has altered the walls too extensively. It is therefore of interest to note that in only four of these cases has dilatation of the hepatic or common ducts been observed; and three of these occurred in adults not known to have suffered from any symptoms referable to the biliary tract. Dilatation of the ducts has never been seen in infants.

It is somewhat remarkable that, although there is no gall bladder in certain families of birds, of fish, some of the rodents, the deer, camel, rhinoceros, and elephant, important abnormalities in its development are so infrequent in man.

Dévé estimates that in infants two per cent. are totally intrahepatic, but that this condition is never found in adult life as all grades of covering of the viscus by the liver parenchyma are seen, and that there is a regular tendency of the liver cells to recede or atrophy and leave the serosa in contact with the viscus. Brewer found few anomalies in position in an anatomical study

of 100 cases, the commonest being the possession of a mesentery, but this was present in only five per cent. A true left-sided gall bladder with viscus and common ducts both to the left of the falciform ligament is said by Schachner to have been reported thirteen times without transposition of other viscera. Double gall bladders and double cystic ducts have been seen, but are extremely infrequent. Absence of the gall bladder of course necessitates some change in the blood vessels, but anomalies of these are much more frequent and more varied than those of the ducts. The cystic artery may be either absent or distributed to the parenchyma of the quadrate lobe. Unimportant variations in the lobulation of the liver have been frequent; a slight fossa may or may not be present, and therefore there may be no line of demarcation of the quadrate lobe, though the gland is otherwise normal.

It is of interest that no defects in the upper part of the head of the pancreas are described even in the cases in which the larger biliary ducts are absent. Developmentally the liver represents a diverticulum from the ventral side of the entoderm shortly beyond the stomach. Two portions, a cephalic, fairly solid portion, and a caudal hollow one, are early differentiated. The latter, the lumen of which is continuous with that of the duodenum, represents the gall bladder. By a constricting process the ductus choledochus and hepatic duct are formed and remain as the only connection which the cephalic portion or pars hepatica retains with the duodenum. The pars cystica in the meanwhile dilates to form the gall bladder and elongates to establish a cystic duct. One or possibly two ventral evaginations from the entoderm are the anlagen also of the head of the pancreas and appear at about the same time as the liver; therefore one might expect abnormalities of the one gland or its ducts to accompany those of the other. These two buds arise from the ductus choledochus, the left probably atrophying early, but the right eventually forms the duct of Wirsung and the ventral part, or head, of the pancreas. If, therefore, the head of the pancreas is normal while the common duct and gall bladder are absent, this defect is prob-

ably due to an early secondary atrophy of their anlagen. A dorsal bud which arises slightly caudal to the ventral one forms the head and tail of the pancreas and it is an interesting fact that in the case of Blakeway there was a defective budding in this region as well as in that of the ventral portion. The hind gut also was incomplete. Unfortunately all the instances of this rare lesion were reported before extensive microscopic sections were made, and we have no studies revealing the condition of the intra-hepatic bile radicles.

The specimen here shown was removed from the body of a female infant aged one year. The child was normally developed, and well nourished, had

Photograph of liver showing absence of gall bladder and distribution of bile ducts. *a*, common bile duct; *b*, liver; *c*, stomach; *d*, pancreas; *e*, duodenum; *f*, falciform ligament.

had an uneventful history with no record of illness until four days before her admission to the hospital when she had an attack of diarrhoea. The symptoms improved but after a week in the hospital she died rather suddenly.

At autopsy it was decided that death was due to a small patch of broncho-pneumonia and to an exudation of pus in the left pleura. This was small in quantity but widely distributed over the entire pleural surface. On lifting up the liver not a trace of gall bladder could be seen, nor any evidence of previous inflammation. The common duct is not dilated, the papilla of Vater normal in size and position. The hepatic ducts are somewhat anomalous as there are two small ducts from the right lobe which join the common trunk below the three which proceed from the left lobe. The hepatic artery and portal vein are normal. There is a slight groove in the liver marking the right margin of the quadrate lobe. The pancreas is normal. Other deformities or abnormalities were not found.

Microscopic sections of the liver show normal lobulations but unusually wide fibrous portal canals in which the bile ducts even at the periphery of the gland are much dilated and lined with tall columnar epithelium. There is no inflammatory lesion. The parenchyma shows a very severe grade of fatty infiltration as about half of each lobule stains heavily with Scharlach R, and the normal liver cells are here apparently entirely destroyed.

CONCLUSIONS

A case of congenital absence of the gall bladder in an infant is presented. No symptoms referable to this lack were observed during life.

The hepatic ducts in this instance have an anomalous distribution but neither they nor the common duct are dilated. The intrahepatic bile ducts are dilated and the liver shows widespread fatty infiltration.

Possibly forty other cases of this defect have been described, about half of them in infants.

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MITOCHONDRIA IN TUMORS

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The motive for this study of mitochondria in tumors arose from a desire to obtain a method of determining the death of a cell after radiation. As you all know, it is perfectly easy to determine the death point of a mouse tumor by inoculating the tumor into another mouse and seeing whether the tumor grows or not, but it is not possible to determine the lethal dose in man without waiting until the patient either dies of the tumor or shows metastases. So this study was begun to attempt to obtain some means of estimating whether the cells of a human tumor have been killed by a given dose of radiation. If such a morphological criterion could be obtained it would be very easy to give accurate dosage to human tumors, for by excising a small piece after raying we could determine whether the cells were dead or not. If not, more x -ray might be given.

Evidently the first thing to do is to determine the normal mitochondrial morphology of the tumors used. The technique is rather laborious, and the demonstration of mitochondria is not

constant. They may be visible in certain groups of cells or in certain parts of the section, but occasionally the method fails in material in which we know there has been no error in technique. It has been said that in sarcomata in man the chondriosomes were usually in the form of rods, and in carcinomata they formed small granules, staining much less deeply than in sarcomata. That is not true of animal tumors, as you will see from the drawings, because the first specimen is a sarcoma, and the granules are exceedingly small. They lie outside of the division figures, and are distributed at random throughout the cell, and often collect at either end of the poles of the nucleus.

These drawings show tumors which have been rayed with large doses, and one of these immediately after the raying shows no change except possibly a slight change in the rods of the chondriosomes. The cells are swollen, an alteration in the cell probably due to changes in the cell membrane in those cells which have been killed. In other tumors it is not possible to tell that the tumor had been rayed at all. In other words, the chondriosomes were exactly what are considered normal. They were taken only twenty-four hours after the exposure. Such exposed tumor cells remain in a viable condition for six or eight days after the dose has been given, and then die. But a determination of the cell death within twenty-four or forty-eight hours would be a great advantage, because we cannot give a large pre-operative dose to a human tumor and permit the patient to wait until there is a deep burn. The tumor must be excised within forty-eight hours at most when such large doses are given, because otherwise serious pain and large sloughs will occur. So this mitochondria method, if it is to be of value, must give an answer within seventy-two hours at the outside. That sufficient morphological changes occur in mitochondria after a lethal dose of x -ray to permit of an estimation of the effectiveness of the application is, so far as our work has gone, doubtful.

HISTOLOGICAL STUDIES OF TUMOR CELLS AFTER X-RAY. I. PRELIMINARY REPORT ON THE MITOCHONDRIA AND DEGENERATION VACUOLES

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The large and rapidly growing literature on x -ray therapy elicits the importance of establishing the lethal x -ray dose for malignant growths and the various efforts at standardization that have been made mostly by physical methods employing ionization chambers and the crystal spectroscope. Although a biological calibration has been attempted, little attention has been paid to the histological phase, the reactions of the cells. The first systematic effort along this line was made by Becton and Colwell in 1911, but since the development of x -ray apparatus of much higher voltage, their work seems inapplicable to-day.

It has long been known that the mitochondrial content varies with the metabolic activity of the cells, decreasing progressively during the last stages of cytomorphosis and increasing at the height of activity. The abundance of mitochondria in embryonic tissue, the relative increase in thyroid cells during hyperthyroidism, and the complete absence during senility of cells (Cowdry, Lewis and Lewis, Duesberg, Goetsch) are examples of such alterations. The neutral red bodies or degeneration vacuoles (Lewis, 1919), on the other hand, tend to increase in the dying cell as long as it remains viable.

Our work of which this is a cursory report employs the cytoplasmic inclusions, the mitochondria and neutral red bodies as criteria of cell reaction and cell injury after x -ray with the hope of throwing some light on the lethal tumor dose.

The examination of fresh tissue, when supplemented by an examination of fixed material and transplantation into the living animal, constitutes the method of choice for the study of mitochondria specifically stained by Janus green, and of the degenera-

tion vacuoles stained by neutral red. Such a method has the advantage of studying tissue which is alive, or that which has undergone little alteration after removal from the host. Besides the technique is simple and rapid (Prigosen, 1921). Our procedure in these experiments briefly stated is as follows: A group of six animals is subjected to the x -rays for varying periods of time. Each animal as well as the control is anesthetized, a wedge of tumor tissue excised, a piece of which is dropped into warm Locke solution; another fixed and the remainder inoculated into twelve animals. On the successive days as long as the animals survive bits of tissue are removed and examined.

A careful histological study by this method of normal unrayed tumors designated numbers 180, R10, R9, R8, JRS, FRC, etc., at the Crocker Institute of Cancer Research revealed the facts that mitochondria are demonstrable by Janus green, but are less responsive than those of lymphocytes; they resist penetration of the dye, the maximum coloration appearing one hour after the application of the dye solution. Since most of these tumors undergo necrosis very readily neutral red bodies are found in small and varying numbers in the dying cells; the number depending upon the integrity of the tumor at the time of examination. Only occasionally are tumor cells impermeable to the stains.

In number, morphology, and cytoplasmic distribution, the mitochondria of tumor cells resemble those of embryonic tissue. The morphology of mitochondria varies, the granular forms predominate in most of the tumors, grouped to form bead-like chains. Definite rods are manifest only in the spindle cells of tumor R10, a polymorphous sarcoma. A delicate pleomorphic form resembling a Pfeiffer bacillus is frequently encountered in the cells of tumor No. 180. The mitochondria are uniformly distributed throughout the cytoplasm; no definite polarity being observed. Occasionally there is a heaping up of the mitochondria at one point close to the nucleus suggesting an intimate relationship with the Golgi apparatus which is believed to be associated with the secretory function of benign cells. Tello, who employed

the uranium nitrate method for the demonstration of the Golgi apparatus and incidentally of the mitochondria, found that in carcinomata depolarization does occur as the tissue becomes malignant.

The study of mitochondria and neutral red bodies in tumor cells after x -ray is now under way and although only a limited number of groups of tumors, No. 180, R10, R9, R8, R39, JRS, IRS, etc., have been exposed to graduated sublethal doses of filtered rays, it appears that a definite diminution in the number of mitochondria within the cell and the number of cells showing mitochondria does take place. This diminution is most noticeable forty-eight hours after exposure.

Material extirpated immediately and twenty-four hours after raying shows relatively little change in the cytoplasmic inclusions but occasionally an edema or cloudy swelling of the cells is observed. The cells appear large and swollen, the nucleus becomes invisible and the cytoplasm has a homogeneous ground glass appearance.

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Discussion:

DR. EWING: I have been very much interested in this effort to establish a lethal sign in rayed tumor cells. It is a question that comes up constantly to one who is studying material of this sort, and one to which we would very heartily welcome an answer. I myself am often unable to give an opinion on the material which I see whether the cell has received a lethal dose or not. It is very difficult to say on morphological data whether a given cell as seen under the microscope is dying or destined to die. I would like to ask Dr. Wood whether the mitochondria demonstrated in these slides are identical with the ordinary mitochondria of normal cells, or whether it is possible that changes brought about by raying may cause an extensive transformation of the original cytoplasm, and a reappearance of granules in new forms, some of

which might give reactions attributed to the mitochondria. Do you regard these bodies as exactly the same as those which Becton described? I believe he abandoned his claims after a longer experience. The subject seems to me however very interesting and suggestive, and I might say that from my point of view it would make very little difference whether Dr. Wood has found the right clue or not. Probably somewhere in this field of morphology a clue will be found. This method appeals to me rather more than the original suggestion of Dr. Wood that we submit our tissues to the biological test. That I think is very difficult, whereas if we could point out some specific morphological change which occurs early in the course of necrobiosis of radiated cells it would be extremely valuable.

DR. PRIGOSEN: There is nothing to add to the discussion, except that I think that the neutral red bodies may possibly prove more useful as indicators of cell injury than the mitochondria. Such degeneration vacuoles may afford better evidence than the mitochondria, but we are not prepared to make a definite statement at the present time.

DR. WOOD: I have been disappointed that the mitochondrial changes did not prove as useful as had been hoped. However, one must be accustomed to disappointments in tumor research, and so I am rather acclimated to negative results. Of course the study of fresh tissues is the phase which is important, as fixation methods take a long time. My hopes are still that within seventy-two hours after raying we will get some type of degeneration or change in cell morphology which will give us a hint which is sufficiently constant to be used as an indicator of approaching cell death.

Dr. Ewing referred to the methods of cell morphology as appealing to him more than the biological tests. By that I presume he means the implantation of tumors after raying. That method of course requires a very long time of waiting, but after all it is the fundamental and only final method, and nothing else will replace it. We have to watch our animals three months to be sure a tumor will not appear after an inoculation has taken place, because the cells are very seriously damaged, and do not grow immediately. The method, even though time-consuming, is the only test of the fact that the cell is dead or alive. Those interested in the treatment of human tumors do not seem to realize that the same method is used in man. If the human tumor grows after radiation, it is not dead; if it does not grow within a period of five or six years, one may properly assume that radiation has killed it. The only difference is that tumors in mice grow so much more rapidly that we can learn whether they have been killed or not in a few months. I hope that next year we can report that we have something of value, either mitochondria, or the neutral red bodies, or some of the other minute cytological structures which our new histology has brought out. So far we have done a large amount of work with very little result.

MULTIPLE HOMOLOGOUS TUMOR TRANSPLANTATIONS AND THEIR BEARING ON THE GENETIC PROBLEMS OF SUSCEPTIBILITY AND IMMUNITY. A PRELIMINARY REPORT

FRANCIS CARTER WOOD, M.D., AND M. R. CURTIS, PH.D.

(From Columbia University, Institute of Cancer Research, F. C. Wood, Director)

That the genetic constitution of animals is an important factor in determining the success of inoculations of grafts from a transplantable tumor should logically have been predicted from the long known facts that a tumor rarely grows when transplanted into animals of species other than the host and that races and strains of the same species respond differently to tumor inoculation. Later contributions based on transplantation into pedigreed stock are important. However the assumption made by some biologists that the genetic susceptibility of the host is the only factor concerned in the fate of a tumor graft is quite as narrow a point of view as to disregard such susceptibility altogether.

That the genetic constitution of the animal is often not the deciding factor in determining either the inoculation outcome or the rate of growth of resulting tumors has been shown by a series of experiments at the Crocker Institute of Cancer Research. In these experiments each of several hundred mice were inoculated simultaneously in four different sites (both axillæ and both groins) with grafts from Crocker Fund mouse sarcoma No. 180. Now it is fairly obvious that the genetic constitution of these four sites in any particular animal is the same, yet the inoculation did not result either in four tumors of equal size or no tumor as would be expected if the genetic factor was the all important one. Of the 413 animals which lived for two weeks after inoculation only one failed to produce any tumor; 5 produced only one tumor; 20 produced two tumors; 95 produced three tumors and 292 produced four tumors. Only the one

animal which failed to respond to all four inoculations could be considered immune, yet of the 1,652 grafts, 154 failed to grow, that is, although only 1 of 413 animals, or 0.24 per cent., was immune, 9.32 per cent. of the inoculations were unsuccessful.

The 413 animals were in five series. The material for the inoculation of each series was selected from a single tumor and care was taken to insure the distribution of the grafts so that two sites in the same animal were no more likely than any other two sites in the series to receive grafts which were contiguous areas of this tumor. Each series showed successful and unsuccessful inoculations, the respective proportions of which may be represented by p and q . If the individuality of the animal had nothing to do with the fate of the graft so that a graft was as like to grow in one animal as in any other we would expect the successful and unsuccessful inoculations to be distributed into n groups of 4 (n being the number of animals in the series) according to the laws of chance. That is, the most probable expectation of 4, 3, 2, 1 and 0 tumors would be represented respectively by the five terms of the binomial $n(p + q)^4$. For each of the five series this theoretical distribution was calculated and compared with the observed distribution by Pearson's¹ method for testing goodness of fit and the probability in 100 trials of a fit as bad or worse than the one observed was determined. These probabilities for the five series were respectively 96.5, 78.0, 64.9, .4, and .0009. That is in three of the five series the theory of a chance distribution of the successful and unsuccessful inoculations fits the observed facts very well. By combining the theoretical distributions for the five series we have as the sum of the most probable expectations² of 4, 3, 2, 1 and 0 tumors 287.4, 101.0,

¹ Tables for Statisticians and Biometricians, London, 1914.

² If we calculate the most probable expectation of 4, 3, 2, 1 and 0 tumors on the basis of an even distribution of takes and non-takes throughout all the experiments, that is, with $p = 1498/1652 = .90678$ and $q = 154/1652 = .09322$, we would have as our most probable expectation in 413 animals the five terms of the binomial $413 (.90678 + .09322)^4$ or 279.23, 114.82, 17.71, 1.21 and .03. This distribution differs significantly from the one observed but since the five series differ from one another in the percentage of successful inoculations the grouping together of the data is not warranted. That is, the difference between

21.0, 3.3, and .3. Figure 1 shows the graphic comparison of this sum of the theoretical distributions with the sum of the observed distributions or 292, 95, 20, 5 and 1.

NUMBER OF ANIMALS

FIG. 1. Broken line = observed frequency in the five series combined. Solid line = sum for the five series of the frequencies expected if chance determined the grouping of positive and negative inoculations.

That this more nearly describes the observations than the theory of four tumors or no tumor is obvious.

Further the two, three, and four tumors in the same individual series leads to a spurious probability of the grouping of successful or unsuccessful inoculations in any animal selected at random. Nevertheless this distribution more nearly fits the one observed than the grouping of four tumors or no tumor expected if the susceptibility or immunity of the animal decided the fate of the graft.

vidual were not of equal size when the experiments were concluded and the animals killed two weeks after inoculation. In four of the five series the tumors were removed and weighed, while in the fifth series the mean diameter was used as a measure of size. A statistical study was made of these data. For each series the correlation coefficients were calculated between the size (measured by weight in the four series and by mean diameter in the fifth series) of

1. Right axillary and left axillary tumors.
2. Right axillary and right groin tumors.
3. Right axillary and left groin tumors.
4. Left axillary and right groin tumors.
5. Left axillary and left groin tumors.
6. Right groin and left groin tumors.

These coefficients or their ratio to their probable errors tell us whether or not the tumors in two different sites in one animal were more nearly the same size than tumors from the same sites in other animals in the series. There were thirty of these coefficients, *i.e.*, six for each of the five series. Sixteen of these were positive and more than three times their probable error and therefore probably significant. Six were positive and between two and three times their probable error. Seven were positive and less than twice their probable error, while one was negative. The absolute values of the significant coefficients were a long way from $+1$, the coefficient of perfect correlation theoretically expected if all the tumors in each individual were the same size. The five highest coefficients were $.521 \pm .051$, $.498 \pm .053$, $.443 \pm .063$, $.430 \pm .076$ and $.427 \pm .095$. These results indicate that the tumors in the same individual were in general more nearly equal in size than would be expected if their association was due to chance. However, other factors reversed this relationship between the tumors from two sites in a particular series.³

The results of this set of experiments force us to the conclusion that there are probably many factors which determine

³ In series 180/86 G' the correlation coefficient between the weights of left axillary and left groin tumors was $-.281 \pm .117$.

the fate of a tumor graft and that the physiological or anatomical peculiarities of the host which include but are not necessarily confined to its genetic constitution are not necessarily the deciding ones.

THE SALT METABOLISM OF TUMORS

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The present paper is a preliminary report; the full paper appeared in the *Journal of Cancer Research*, 1922, vii, 417.

In an attempt to further elucidate the peculiar behavior of tumor-bearing rats with reference to the carbohydrate metabolism after the injection of protein,¹ microchemical examinations of various types of benign and malignant tissues were made. Among the various chemical substances sought for in both benign and malignant cells were the various salts, which were stained according to the methods described by Macollum. In confirmation of the work of others, irrespective as to the type of cell, *i.e.*, benign or malignant, actively proliferating or quiescent, the potash was found to be present in the cell cytoplasm and pericellular fluids, the calcium in the nucleus, cytoplasm and pericellular fluids, and the soda in the pericellular fluids. The phosphates were found in the cytoplasm and nucleus, and occasionally in the pericellular fluids, while the chlorides and sulphates were found only in the pericellular fluids and the cell wall.

Estimation of the salt deposit in the microscopic preparations indicated that receding tumors contained less potash and more calcium than did growing tumors, apparently confirming results obtained by Beebe and Buxton, and Clowes and Frisbie. In addition it was noted that there were more cells per given area in a receding than in a similar area of growing tumor.

Estimations of the potash, soda, and calcium content of the blood of animals bearing transplanted progressively growing

¹ For a report of these experiments, see *Jour. Cancer Research*, 1921, vi, 223.

tumors, and of the same tumor strain undergoing spontaneous recession, as well as of the blood of animals bearing spontaneous liver tumors, were made after the method described by Kramer and Tisdall. In a similar manner the salt content of the tumors themselves and of other tissues of the body not involved in the tumor process was also determined.

It was found that the parenteral introduction of living homologous cells, irrespective as to whether these cells were malignant or benign, caused a demineralization of the blood, and that the same condition occurred when malignant cells arose in the host *de novo*. When the cells which had been introduced died, *i.e.*, the tumor spontaneously receded, there occurred a hypermineralization of the blood which in turn disappeared when the dead cells were completely absorbed. This occurred irrespective as to whether the cells that were dead were benign or malignant.

While these changes were going on in the blood an analogous series of changes was occurring in the testes. As the transplanted tumor grew the testes became demineralized, and as the tumor receded, the organ became hypermineralized, to return to the normal when the tumor had been completely absorbed. The transplanted tumors themselves showed marked demineralization during the process of recession. When the tumors were spontaneous in origin the organ in which the growth arose showed a hypermineralization more marked than that which took place in the tumor itself.

With these changes in the total salt content there also occurred a change in the ratio of the various salts. When living cells (irrespective as to whether they are benign or malignant) were parenterally introduced, both the potash and soda ratio, as compared with the calcium in the blood stream, were reduced. When these cells died, the potash partially returned to the normal ratio, while the soda exceeded the normal ratio by as much as 100 per cent. The ratio in the blood of spontaneous tumor-bearers is analogous to that found in those bearing spontaneously receding transplanted tumors, a fact probably explainable by the large amounts of dead tissue present in spontaneous tumors.

When the ratio of potash to soda is taken, there is evident a marked increase in the soda in the blood of those bearing receding transplanted or spontaneous tumors.

In the tissues not involved in the neoplastic process a similar series of changes is observed. The introduction of living cells caused in the testes a reduction of both potash and soda when compared with the calcium, while when the introduced cells died and were absorbed there was a partial return to the normal. In the liver in which a spontaneous tumor has developed, there was a reversal of the normal, for while in the normal there is twice as much soda as potash, in the spontaneous tumor liver the potash and soda were about equal. In both spontaneous and transplanted growing tumors the potash and soda were about equal in ratio when compared with calcium, while in the receding tumors the soda ratio was very markedly increased.

From the results of the experiments it appears that the introduction of homologous living cells, whether benign or malignant, causes a demineralization of the blood and body tissues with a storing up of these elements in the growing cells. When the inoculated cells die the stored up mineral is again delivered to the blood and returned to the tissues. When the new cells develop in the host, *de novo*, the same demineralization of the blood occurs with a storage of the salts, not alone in the developing tumor, but also in the organ in which the tumor arises. With these changes there occurs a disturbance of the ratio of the salts in their relation one to the other, most of the increase being in soda, and the decrease in potash.

Other experiments which will not be detailed here indicate that these changes are secondary to the growth and death of the cells and have no relation to either the genesis or spontaneous recession of the tumors.

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